Supreme Court, U.S.
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No. 03-1586

IN THE

Supreme Court of the United States

ANDREW BOURNE, a minor by and through his parents, next friends and natural guardians, CHRIS BOURNE and MAGGIE BOURNE,
Petitioner,

v.

E.I. DUPONT DE NEMOURS & COMPANY,
Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

RESPONDENT'S BRIEF IN OPPOSITION

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QUESTION PRESENTED

Whether the United States Court of Appeals for the Fourth Circuit correctly affirmed the district court's decision to exclude expert testimony where that testimony was based on speculative extrapolations from *in vivo* and *in vitro* studies that failed to meet the reliability and relevance standards under Federal Rule of Evidence 702.

CORPORATE DISCLOSURE STATEMENT PURSUANT TO RULE 29.6

Respondent E.I. du Pont de Nemours and Company ("DuPont") has no parent company, and no publicly held company owns 10% or more of DuPont's stock. DuPont is a publicly traded corporation listed on the New York Stock Exchange.

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IN THE

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E.I. DUPONT DE NEMOURS & COMPANY,
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RESPONDENT'S BRIEF IN OPPOSITION

STATEMENT OF THE CASE

This is a products liability case in which Petitioner Andrew Bourne alleges that his ocular and other birth defects were caused by his mother's dermal exposure to Benlate while she was pregnant. Benlate is a plant fungicide manufactured by DuPont and sold worldwide for more than 30 years.

Pursuant to Federal Rule of Evidence 702, DuPont moved to exclude the testimony of Petitioner's causation experts, Drs. Howard and Tackett. DuPont explained that Drs. Howard's and Tackett's asserted methodology for determining the human teratogenicity of a substance was specula-

tive, scientifically invalid, unreliable, and not relevant. Following briefing, and agreement by the parties that the record was complete and a hearing was not needed, the district court granted DuPont's motion without a hearing.

In a Memorandum Order dated January 11, 2002, the district court held that Petitioner's experts' method of attempting to extrapolate causation of human birth defects from single-species, high dose gavage animal (rat) and *in vitro* (cell culture) studies was neither reliable nor relevant. Petitioner then requested, without objection from DuPont, that the evidentiary deposition of an epidemiologist, Dr. Ozonoff—another designated expert of Petitioner—be made a part of the record and considered by the court. After granting Petitioner's request and considering Dr. Ozonoff's testimony,[1] the district court reissued its Memorandum Order, revised in minor respects to reflect its further consideration of Dr. Ozonoff's testimony, and granted DuPont's motion to exclude on the same basis set forth in its original order. *See Bourne v. E.I. DuPont de Nemours & Co.*, 189 F. Supp. 2d 482, 496-501 (S.D.W. Va. 2002), Pet. App. at 71-84. Absent proof of causation for Petitioner's claim, the district court granted DuPont's motion for summary judgment and dismissed the case.

Petitioner appealed to the United States Court of Appeals for the Fourth Circuit. The court of appeals concluded that in "excluding the proffered testimony, the district court properly exercised its 'gate-keeper' function by focusing on the methodology employed by the expert rather than the conclusions they reached . . . we can not say that the district court abused its discretion." *See Bourne v. E.I. DuPont de Nemours*, No. 02-1469, slip op. at 6 (4th Cir. Jan. 27, 2004)

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[1] As the January 11, 2002, order reflects, the district court had already considered Dr. Ozonoff's views (based on an earlier discovery deposition). *See* January 11, 2002 Memorandum Order at 21-23.

(*per curium*), Pet. App. at 7. On that basis the Fourth Circuit affirmed the decision of the district court excluding the testimony of Drs. Howard and Tackett. *Id.* Petitioner filed a petition for rehearing which was denied on February 23, 2004.

This petition followed.

REASONS FOR DENYING WRIT

The Court should decline to grant the petition for a writ of certiorari. The district court properly exercised its "gatekeeper" function in finding that the Petitioner's experts' proposed method of extrapolation of human teratogenicity from single-species, high dosage gavage rat tests and *in vitro* tests was unreliable and lacked "fit." This case does not present the question that Petitioner advertises—even assuming that such a question would warrant certiorari. Contrary to Petitioner's assertions, the court of appeals' decision does not require "positive" epidemiology as a basis for expert opinion testimony concerning causation in a toxic tort case. Even if the court of appeals had required "positive" epidemiology in this case, such a holding would not conflict with the decisions of other federal courts of appeal in *teratology* cases.

I. THE DISTRICT COURT PROPERLY EXERCISED ITS "GATEKEEPER" FUNCTION IN FINDING THE PROPOSED METHOD OF EXTRAPOLATION OF HUMAN TERATOGENICITY FROM SINGLE-SPECIES, HIGH DOSAGE GAVAGE RAT TESTS AND *IN VITRO* TESTS UNRELIABLE AND LACKING IN "FIT".

As the district court observed, "Drs. Howard and Tackett have derived their general causation theory, that benomyl is teratogenic to humans, based solely upon *in vivo* rat gavage studies and *in vitro* tests." *Bourne*, 189 F. Supp. 2d at 495, Pet. App. at 71. The district court then identified the scien-

tific and factual shortcomings of the methodology that they had used. These included:

- Significant differences between species in teratogenic response to chemicals. *Id.* at 496–97, Pet. App. 73–75.
- Petitioner's experts' disavowal of and inability to explain the results of benomyl tests on two other animal species—rabbit and mouse—that showed no ocular birth defects in the offspring. *Id.* at 496–97, Pet. App. at 73–75.
- The absence of tests on species closely related to humans. *Id.* at 496–97, Pet. App. at 72-75.
- The use of high dosages in the rat tests, far in excess of human exposures. *Id.* at 498-99, Pet. App. at 76-78.
- *In vitro* test exposures at high levels for 24 hours, far in excess of human exposures. *Id.* at 498-99, Pet. App. at 76-78.
- A mode of exposure, direct injection into the stomachs of rats, unlike the human dermal exposure that was at issue in this case. *Id.* at 498-500, Pet. App. at 76-83.
- Petitioner's experts' unfounded rejection of human data contrary to their position. *Id.* at 493, 495, 497, Pet. App. at 72-73, 75-77, 80-83.

The district court discussed the fact that teratologists (and other courts) have rejected *in vivo* animal and *in vitro* tests as a basis for finding human teratogenicity in birth defect cases.[2]

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[2] *See also* Anthony R. Scialli, *A Clinical Guide to Reproductive and Developmental Toxicity* at 60-61 (1992) (teratologists do not accept positive results in animal tests as proof of human teratogenicity because there are (1) species differences in the pharmacokinetics/handling of chemicals (difference in absorption, distribution, metabolism, elimination); (2) species differences in fetal and embryo susceptibility, and (3) differences in

Id. at 496-97, Pet. App. at 73-77. This analysis of the facts, science, and law relating to the methodology employed by Petitioner's experts—extrapolation of human teratogenicity from single-species, high dosage gavage animal tests and *in vitro* tests—is precisely the kind of "gate-keeping" contemplated by this Court's *Daubert* decision. The court of appeals opinion recognizes that the district court's "well-reasoned opinion" reflects the type of "gate-keeping" that this Court's decisions mandate. *See Bourne*, slip. op. at 6, Pet. App. at 7.

II. THE PETITION INCORRECTLY ASSERTS THAT THE COURT OF APPEALS CREATED A RULE REQUIRING EPIDEMIOLOGY TO BE THE BASIS FOR EXPERT OPINION TESTIMONY CONCERNING CAUSATION IN TOXIC TORT CASES.

Petitioner asserts that this case presents the question "whether *Daubert* requires positive epidemiology to support a finding of causation in a toxic tort case." Petition at 7. That assertion misstates the holdings of both the district court and the court of appeals. Neither court held that epidemiological evidence was a prerequisite to expert opinion testimony on causation in such cases.

The district court did not require epidemiological evidence as a basis of expert opinion testimony offered as proof of causation in this case. Rather, the district court focused on the specific methodology employed by Drs. Howard and Tackett—extrapolation of human teratogenicity from rat gavage tests and extrapolation of human teratogenic dose levels from *in vitro* cell tests—and held that such extrapolation was unreliable and irrelevant. *Bourne*, 189 F. Supp. 2d at 496, 497-54 (Pet. App. 72, 73-84). Epidemiological evi-

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the dose and route of exposure (*e.g.*, gavage v. dermal) as between humans and laboratory test animals).

dence would present a way of bridging the gap the court correctly saw in Petitioner's methodology in assessing causation, but nowhere did it hold that epidemiology was mandated. It held that what was presented by Petitioner's experts was not acceptable because it was unreliable and irrelevant. The court of appeals, without referring to epidemiology at all, approved the district court opinion as "well reasoned" and held that that "the district court properly exercised its 'gate-keeper' function by focusing on the methodology employed by the experts rather than the conclusion they reached." *Bourne*, slip. op. at 6, Pet. App. at 7.[3]

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[3] While it was not the basis for the district court's exclusion of Drs. Howard's and Tackett's opinion testimony or the basis for the court of appeals' decision affirming that exclusion, the absence of any human evidence of Benlate teratogenicity reflects a major methodological failure in the derivation of Petitioner's experts' opinions. The generally accepted, peer reviewed, methodology employed by clinical teratologists requires positive human studies to establish human teratogenicity of a substance, as numerous trial courts have recognized. *See Wade-Greaux v. Whitehall Labs., Inc.*, 874 F. Supp. 1441, 1451 (D.V.I.), *aff'd*, 46 F.3d 1120 (3d Cir. 1994); *National Bank of Commerce v. Dow Chem. Co.*, 965 F. Supp. 1490, 1497 n. 14, 1499-1500 (E.D. Ark. 1996), *aff'd*, 133 F.3d 1132 (8th Cir. 1998); *DePyper v. Navarro*, No. 83-303467-NM, 1995 WL 788828, at *32 (Mich. Cir. Ct. Nov. 27, 1995), *aff'd*, No. 191949, 1998 WL 1988927 (Mich. Nov. 6, 1999); *Oxendine v. Merrell Dow Pharms., Inc.*, No. 82-1245, 1996 WL 680992, at *7 (D.C. Super. Ct. Oct. 24, 1996).

Daubert and *Kumho* establish that, in assessing the reliability of expert testimony, a trial court should look to the principles of the discipline or field in which the opinion is being offered. *Kumho Tire Co. v. Carmichel*, 526 U.S. 137, 152 (1999); *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 591-95 (1993); *see also Cavallo v. Star Enterprise*, 100 F.3d 1150, 1159 (4th Cir. 1996) (*Daubert* factors "require that the methodology and reasoning used by a witness have a significant place in the discourse of experts in the field.") The field of teratology requires epidemiology for a determination that a substance is a human teratogen. *See, e.g.*, Thomas H. Shepard, *"Proof" of Human Teratogenicity*, Teratology 50: 97-98 (1994); Thomas H. Shepard, *Catalog of Teratogenic Agents* at xxiv (10th

The Petition does not address the actual holding of the court of appeals or the holdings of the district court which were affirmed by the court of appeals. Nor does the Petition state a question for review that arises from those decisions. The lack of connection between the arguments of Petitioner and the holdings of the courts below is apparent from the following comparison:

Petitioner's Argument As To What The District Court and Court of Appeals Held	Actual District Court Holdings Affirmed By The Court Of Appeals
"Nonetheless, the principal reason the District Court excluded the testimony of Drs. Howard and Tackett was their reliance on Dr. Ozonoff's conclusion that these epidemiological studies were flawed and irrelevant." (Petition at 8)	"[T]he extrapolations of Drs. Howard and Tackett, from high-dosage, single species *in vivo* testing and lengthy benomyl exposure *in vitro* testing, to conclude that benomyl is a human teratogen and to establish the levels at which it is alleged to be teratogenic, are neither reliable, pursuant to the first prong of Daubert, nor relevant, under the second prong."
"[Y]et the District Court used Ozonoff's analysis of the existing Benlate epidemiology as the primary	

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ed. 2001); James L. Schardein, *Chemically Induced Birth Defects*, at 43-44 (3d ed. Rev. 2000), quoting Thomas H. Shepard, *Catalog of Teratogenic Agents* (8th ed. 1998); Robert L. Brent, *Utilization of Animal Studies to Determine the Effects and Human Risks of Environmental Toxicants (Drugs, Chemicals, and Physical Agents)*, Pediatrics 113:984, 987 (2004). If the district court and the court of appeals had recognized such a requirement for expert testimony on the human teratogenicity of a substance, that ruling would have been correct and would not have been an abuse of discretion. The lower courts in this case did not, however, reach that issue and they need not have done so. It was a sufficient basis for their decisions that they examined the methodology in fact used by Drs. Howard and Tackett, rejecting it as unreliable and irrelevant.

basis to exclude Howard and Tackett's testimony." (Petition at 13)

"But in affirming the District Court's decision, the Fourth Circuit, . . . implicitly overruled its own earlier decisions holding that epidemiological support was not a prerequisite to establishing causation in toxic tort cases." (Petition at 7)

(*Bourne*, 189 F. Supp. 2d at 496, Pet. App. at 72)

"The court concludes that Drs. Howard and Tackett have failed to offer sufficient support for the otherwise suspect single species *in vivo* tests and *in vitro* tests to render methodologically sound an extrapolation of human teratogenicity." (*Bourne*, 189 F. Supp. 2d at 497-98, Pet. App. at 76)

"Moreover, the rat gavage studies and the *in vitro* tests relied upon by Drs. Howard and Tackett, using injections of high-levels of benomyl directly into the stomach of rats and high-level *in vitro* dosing of cells of both rats and humans in benomyl for 24 hours, do not 'fit' with the facts of the case as alleged." (*Bourne*, 189 F. Supp. 2d at 498, Pet. App. at 76)

The district court, in arriving at its conclusions, discussed some of the reasons that teratologists do not accept extrapolation of human teratogenicity from animal and *in vitro* tests. *See Bourne*, 189 F. Supp. 2d at 496-98, Pet. App. at 72-77; *see also* discussion, *supra*, at 3-4. In the context of that discussion, the district court noted as well that, "in the

absence of other strong indicators of the reliability of *in vivo* and *in vitro* tests, including supporting epidemiological studies, testing on closely related species, and the use of comparable dosages, courts have overwhelmingly found unreliable the methodology of extrapolating human teratogenicity from *in vivo* and *in vitro* tests." *Bourne*, 189 F. Supp. 2d at 496, Pet. App. at 73. In other words, the court properly recognized that the type of testing done here involving ultra-high doses given to rats by gavage, is not generally accepted as a basis for extrapolating human teratogenicity under the standards of the relevant discipline. Rather, teratologists require additional indicia of reliability, including epidemiology. *See supra* notes 2 and 3. The district court's factual observations that teratologists and other courts reject extrapolation of human teratogenicity from single-species, high dosage gavage animal tests and *in vitro* tests are not holdings by the district court that epidemiology is an essential basis for expert opinion offered to prove causation in a case involving toxic torts; they are recognition that such extrapolation is not generally accepted in the field of teratology. Significantly, Petitioner cites no case under *Daubert* and Rule 702 challenging the court's observation that other courts, like teratologists, do not accept such extrapolation.

Nor was the district court's additional observation that the existing Benlate epidemiological evidence is contrary to Petitioner's position, (*id.* at 497 & n.23, Pet. App. at 75 & n.23), a holding that epidemiology is affirmatively required to demonstrate causation.[4]

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[4] The district court's determination that Drs. Howard's and Tackett's rejection of Benlate epidemiological studies—which find no association between Benlate exposure and birth defects—was unfounded, *Bourne*, 189 F. Supp. 2d at 493, Pet. App. 30, does not constitute a holding by the district court that epidemiology is a prerequisite to proof of causation. The district court ruling that Drs. Howard's and Tackett's rejection of epidemiology that is contrary to their position is unfounded—the sole focus of the Petition—is irrelevant to whether Petitioner's experts could

The court of appeals' affirmance of the district court's actual holdings does not convert these separate factual observations by the district court into rulings by the court of appeals that epidemiology is a prerequisite to opinion testimony on causation in toxic tort cases. Petitioner has mischaracterized the basis for the district court's holding on the unreliability and lack of "fit" of Drs. Howard's and Tackett's methodology. The Petition ignores the fact that the opinion of the court of appeals says nothing, explicitly or implicitly, about the place of epidemiology in proving causation in toxic tort cases. Petitioner's stated questions for review do not arise from and are unrelated to the court of appeals decision in this case.

III. THERE IS NO CONFLICT BETWEEN THE DECISION OF THE COURT OF APPEALS IN THIS CASE AND ANY OTHER CIRCUIT.

There is no circuit conflict.

First, the court of appeals' decision in this case does not require that expert testimony concerning causation in toxic tort cases be based on "positive" epidemiology. The appellate opinion says nothing on that subject. Nor does its affirmance of the district court decision implicitly or "effectively" suggest that result as Petitioner argues. The district court decision excluding the testimony of Drs. Howard and Tackett is based on the fact that their methodology—extrapolation of human teratogenicity from single-species, high dosage gavage animal tests and *in vitro* tests—is unreliable and irrelevant; it is not based on the failure of the experts in this case to rely on "positive" epidemiology. The opinion of the district court does not say or imply that the court is requiring

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properly extrapolate human teratogenicity from rat and *in vitro* tests. Such extrapolation is not a reliable methodology in the field of teratology and the district court properly so held. *See id.* at 497 n.21, Pet. App. at 75 n.21.

experts to base their opinions on "positive" epidemiology in order to prove causation in toxic tort cases. The court of appeals decision cannot, therefore, be in conflict with decisions of other circuits regarding lack of need for "positive" epidemiology in some toxic tort cases.

Second, even if the Fourth Circuit had required "positive" epidemiology, such a holding would not conflict with the decisions of other federal courts of appeal in *teratology* cases. In evaluating the circuit conflict issue that Petitioner seeks to raise, it is important to distinguish teratology cases from other toxic tort cases. Some fields of science or medicine involved in other toxic torts may not in fact rely heavily or at all on epidemiology.[5] That is not the case with respect to teratology. The generally accepted methodology for determining human teratogenicity of a substance involves: (1) identifying a specific pattern of malformation associated with exposure to the substance; (2) consistent human studies (epidemiology) and occurrence of the specific pattern of malformation; (3) repeated positive animal tests in multiple species at doses and routes of exposure similar to those involved in human exposures; (4) *in vitro* tests identifying a mechanism of action; and (5) biological plausibility that the agent's mechanism of action could cause the pattern of defects associated with exposure.[6]

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[5] *See, e.g., Benedi v. McNeil-P.P.C., Inc.*, 66 F.3d 1378 (4th Cir. 1995) (where issue was whether liver damage was caused by Tylenol/alcohol consumption or by herpes, epidemiology was unnecessary and a methodology consisting of identifying a history of Tylenol/alcohol use, laboratory tests showing presence of Tylenol in blood, and microscopic examination of liver tissue samples to confirm whether tissue damage was or was not characteristic of damage caused by Tylenol was acceptable for diagnostic purposes concerning causation).

[6] *See* Thomas H. Shepard, *"Proof" of Human Teratogenicity*, Teratology 50:97-98 (1994); Thomas H. Shepard, *Catalog of Teratogenic Agents* at xxiv (10th ed. 2001); Robert L. Brent, *Utilization of Animal Studies to Determine the Effects and Human Risks of Environmental*

The case law of the various circuits is uniform in acknowledging that epidemiology is an essential basis for expert opinion testimony concerning causation in *teratology* cases.[7] Thus, even if the Fourth Circuit decision in this case were interpreted to require that expert opinion in the field of teratology be supported in part by epidemiology, that interpretation would create no conflict among the circuits.

Third, none of the cases cited by Petitioner demonstrate any controversy about the role of epidemiology in *teratology* cases. With two exceptions, those cases do not involve expert testimony in the field of teratology. One exception is *Ambrosini*.[8] While it is a teratology case, it provides Petitioner no support for his argument that there is a conflict in the circuits. In *Ambrosini*, there was "positive" epidemiology indicating an association between the type of drug involved, a progestin, and birth defects; the plaintiff's expert so asserted in an affidavit filed in opposition to a motion for

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Toxicants (Drugs, Chemicals, and Physical Agents), Pediatrics 103:984, 987 (2004); James L. Schardein, *Chemically Induced Birth* Defects at 44 (3d ed. Rev. 2000); Anthony R. Scialli, *A Clinical Guide to Reproductive and Developmental Toxicology* at 60, 65, 84 (1992); James C. Wilson, *Embryotoxicity of Drugs in Man, in the Handbook of Teratology* at 311-12 (1977) (James C. Wilson and F. Clarke Fraser, eds.); *Wade-Greaux, Inc.*, 874 F. Supp. at 1450-55; *National Bank of Commerce v. Dow Chem. Co.*, 965 F. Supp. at 1497 n. 14, 1499-1500; *see also* cases cited in note 7, *infra*.

[7] *See Raynor v. Merrell Pharm, Inc.*, 104 F.3d 1371, 1375 (D.C. Cir. 1997); *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1321 (9th Cir. 1995) (Daubert II); *Ealy v. Richardson-Merrell, Inc.*, 897 F.2d 1159 (D.C. Cir. 1990); *Wilson v. Merrell Dow Pharm.*, 893 F.2d 1149, 1154 (10th Cir. 1990); *Brock v. Merrell Dow Pharm., Inc.*, 874 F.2d 307, 313 (5th Cir.), *modified on reh'g*, 884 F.2d 166 (1989); *Richardson v. Richardson-Merrell, Inc.*, 857 F.2d 823, 830-31 (D.C. Cir. 1988); *Lynch v. Merrell-National Lab.*, 830 F.2d 1190 (1st Cir. 1987); *cf. Elkins v. Richardson-Merrell, Inc.*, 8 F.3d 1068, 1071 (6th Cir. 1993); *Turpin v. Merrell Dow Pharm., Inc.*, 959 F.2d 1349, 1360 (6th Cir. 1992).

[8] *Ambrosini v. Labaraque*, 101 F.3d 129 (D.C. Cir 1996).

summary judgment.[9] *Ambrosini* specifically relied on the fact the plaintiff experts had based their conclusions concerning causation of birth defects on "human" (epidemiological) evidence.[10] Thus, anything the *Ambrosini* court may have said about the lack of necessity for epidemiology[11] was *dicta* unrelated to the decision in the case. Indeed, in *Ambrosini* the D.C. Circuit discussed its prior *Richardson* decision with approval.[12] That case held that animal tests, *in vitro* tests, and recalculated epidemiology studies that are at odds with the underlying epidemiology studies are not relied on by experts in the field of teratology.

The only other teratology case cited by Petitioner to suggest a conflict in the circuits, *Turpin*, is not about "positive" epidemiology or about failure of plaintiff experts to rely on "positive" epidemiology to prove causation in a teratology case.[13] The epidemiology in that case was 35 negative studies relied on by defendant to demonstrate no causal relation between the drug Bendectin and birth defects. *Turpin* did not hold that plaintiff experts need not rely on epidemiology; rather, *Turpin* held that defendant's epidemiology studies in that case were not so conclusive that they warranted grant of summary judgment for defendant.[14]

The Fourth Circuit has not yet addressed the issue whether epidemiology is a required basis of expert testimony concerning causation in a teratology case. Neither of the Fourth Circuit cases cited by Petitioner to suggest a conflict within

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[9] *Id.* at 132, 136, 139.

[10] *Id.* at 141.

[11] The material quoted by Petitioner as if it were from *Ambrosini* is actually from another case, *Ferebee v. Chevron Chemical Co.*, 736 F.2d 1529 (D.C. Cir. 1984), which is not a teratology case.

[12] *Ambrosini*, 101 F.3d at 138, 140.

[13] *Turpin v. Merrell Dow Pharm., Inc.*, 959 F.2d 1349 (6th Cir. 1992).

[14] *Id.* at 1353-57.

the Fourth Circuit's own case law—*Westberry* and *Benedi*—are teratology cases. Thus, there would be no conflict in the Fourth Circuit's own case law even had the court of appeals in this case required that expert testimony in teratology cases be based in part on epidemiology.[15]

CONCLUSION

The petition for writ of certiorari should be denied.

Respectfully submitted,

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June 25, 2004

[15] Petitioner's argument (at 20-21) that the "disparate decision" of the Florida Supreme Court in *Castillo* "cr[ies] out for intervention by this Court" to provide guidance and promote uniformity ignores the fact that *Castillo* was decided under the *Frye* standard while the decision in this case was guided by Rule 702 and the *Daubert* standard. Uniformity of decisions under *Frye* and under *Daubert* cannot be expected because of the differences in the two rules and thus, Petitioner's argument from *Castillo* does not support a writ of certiorari.

Supreme Court, U.S.
FILED

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No. _____

In The

Supreme Court of the United States

ANDREW BOURNE, a minor by and through his parents, next friends and natural guardians, CHRIS BOURNE and MAGGIE BOURNE,

Petitioner,

vs.

E.I. DUPONT DE NEMOURS & COMPANY, d/b/a DuPONT, a Foreign Corporation,

Respondent.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Fourth Circuit

PETITION FOR A WRIT OF CERTIORARI

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QUESTIONS PRESENTED FOR REVIEW

Petitioner/Plaintiff alleged in this products liability case that his mother's dermal exposure to Benlate, a fungicide manufactured by Defendant, caused him to be born with a rare birth defect – anophthalmia – the complete absence of eyes. Plaintiff's mother's exposure to Benlate occurred during the period of organogenesis when the eyes develop. The District Court excluded the testimony of Plaintiff's "credible and qualified" expert teratologist and pharmacologist, where it concluded that they had improperly relied upon the opinion of an unchallenged expert epidemiologist who had discounted the reliability of flawed studies used by Defendant to show the lack of epidemiological support for a finding of general causation. The District Court focused on and overruled the conclusions reached by the unchallenged epidemiologist, rather than focusing on the methodology employed by Plaintiff's teratologist and pharmacologist.

The Questions Presented Are:

1. Whether the Court of Appeals erred in upholding the decision of the District Court, which excluded the testimony of Plaintiff's expert teratologist and pharmacologist, in large part by focusing on and overruling the *unchallenged* conclusions of an *unchallenged* epidemiologist upon whose opinions Plaintiff's experts relied, rather than focusing on the methodology employed by Plaintiff's experts.

2. Whether the Court of Appeals erred in upholding the decision of the District Court, which held that Plaintiff's experts could not demonstrate causation based on extrapolation from *in vivo* animal studies, *in vivo* human dermal absorption and *in vitro* studies in the absence of "positive" epidemiology.

LIST OF PARTIES TO PROCEEDINGS

All parties are identified in the caption.

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PETITION FOR A WRIT OF CERTIORARI

ANDREW BOURNE, a minor by and through his parents, next friends and natural guardians, CHRIS BOURNE and MAGGIE BOURNE, respectfully petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Fourth Circuit.

OPINIONS BELOW

The opinion of the United States District Court for the Southern District of West Virginia excluding Plaintiff's experts, entitled *Bourne v. E.I. DuPont De Nemours & Company, Inc.*, and issued on March 29, 2002, is published at 189 F. Supp.2d 482 (S.D.W.Va. 2002) and is reproduced in the appendix (App.) at App. 8.[1] The unpublished opinion of the United States Court of Appeals for the Fourth Circuit affirming the judgment of the District Court, dated January 27, 2004, is reproduced at App. 1. The citation to this unpublished opinion, *Bourne v. E.I. DuPont De Nemours & Company, Inc.*, is 85 Fed.Appx. 964, 2004 WL 117634 (4th Cir. 2004).

The order of the United States Court of Appeals for the Fourth Circuit denying Petitioner's petition for panel rehearing, dated February 23, 2004, is reproduced herewith at App. 85.

[1] On January 11, 2002, the District Court had issued an unpublished Memorandum Order granting DuPont's motion to exclude. This Memorandum Order is reproduced at App. 48.

JURISDICTION

As noted, on January 27, 2004, the United States Court of Appeals for the Fourth Circuit affirmed the decision of the District Court and on February 23, 2004, the Court of Appeals denied Petitioner's petition for rehearing. Petitioner had originally filed this action in West Virginia State Court. The Defendant removed this action to the United States District Court for the Southern District of West Virginia pursuant to 28 U.S.C. § 1441. The basis for the District Court's jurisdiction was 28 U.S.C. § 1331 – federal question – and § 1332 – diversity of citizenship. This Honorable Court has jurisdiction to hear this matter pursuant to 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS INVOLVED

Federal Rules of Evidence, Rule 702 – Testimony by Experts.

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

STATEMENT OF THE CASE

Minor Plaintiff Andrew Bourne was born in England in 1987 with bilateral anophthalmia – the complete absence of eyes – and other birth defects. Twice during the critical period in his fetal eye development, Andrew's mother used Benlate while gardening and was wetted by the Benlate aqueous mixture as she mixed the chemical in water and sprayed it on her plants.

Benlate is an agricultural fungicide manufactured by Defendant E.I. DuPont de Nemours and Company, Inc. (DuPont). Prior to being withdrawn from the market in 2001, Benlate was widely used commercially in many countries. It was sold for residential use in the United Kingdom and elsewhere, but never in the United States. Plaintiff brought this products liability action against DuPont, alleging that his mother's dermal exposure to Benlate during her early pregnancy caused his anophthalmia.

DuPont moved to exclude the testimony of Plaintiff's two causation experts, teratologist and medical doctor Vyvyan Howard and toxicologist Randall Tackett, under *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993) and F.R.Evid. 702. Notably, DuPont did not move to exclude the testimony of Plaintiff's expert epidemiologist, Dr. David Ozonoff. The District Court, ruling exclusively on the written submissions of the parties, granted DuPont's motion.[2]

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[2] The District Court explained that its *sua sponte* revision of its earlier unpublished ruling was necessary to address Dr. Ozonoff's deposition testimony. (App. 9) The revised opinion is markedly

(Continued on following page)

In formulating their opinions that Benlate is a human teratogen that caused Plaintiff's malformations, Plaintiff's experts (primarily Dr. Howard) relied upon a plethora of information, including:

a) Scientific and medical literature on the toxicology and pharmacokinetics of benomyl,[3] the active ingredient in Benlate, and MBC, benomyl's primary metabolite, demonstrating that Benlate's anti-fungal properties stem from its ability to bind to tubulin, and thus interfere with cell division, together with the common scientific knowledge that embryonic cells are rapidly dividing as the conceptus grows;

b) The medical records of Plaintiff and his family and the depositions of treating physicians, geneticists, obstetricians, neuro-radiologists and ophthalmologists;

c) The deposition and an interview of Plaintiff's mother detailing her exposure to Benlate;

d) Numerous gavage reproductive toxicology studies, some peer-reviewed, performed by DuPont and independent researchers, demonstrating an undisputed link between benomyl and anophthalmia in the pups of various strains of rats;

e) DuPont's own rat gavage pharmacokinetics study, demonstrating that benomyl sequesters in the uveal tract of the eye at a level three times greater than the organ with the next highest concentration of benomyl,

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different in its treatment of the epidemiological data from the earlier, unpublished Memorandum Order. Compare *Bourne v. DuPont*, No. 97-0090 Mem. Op. at 20-24 (S.D.W.Va. Jan. 11, 20[illegible]2) (App. 63-67) with *Bourne*, *supra*, 189 F.Supp.2d at 491-93 (App. 25-30).

[3] "Benlate" and "benomyl" are used interchangeably herein.

and that benomyl remains in the uveal tract greater for an extended period of time;

f) Two *in vitro* studies, one published in a peer-reviewed journal, demonstrating cell injury in concentrations a small fraction of what Dr. Howard calculated was absorbed by Plaintiff's fetal eyes;

g) An *in vitro* test on human cadaver skin and two *in vivo* studies on volunteers demonstrating the transdermal assimilation and consequent bioavailability of benomyl and MBC;

h) The EPA's and European Community's classifications of benomyl as a potential developmental toxicant;

i) Their knowledge and experience in the areas of medicine, pathology, developmental toxico-pathology and pharmacokinetics;[4]

j) Three epidemiological studies pertaining to Benlate and the opinion of Dr. David Ozonoff discounting the significance and reliability of those studies;

k) Finally, based upon the forgoing factors, Dr. Howard performed a differential diagnosis, from which he concluded that other known potential causes of anophthalmia and Plaintiff's related malformations, such as chromosomal abnormalities, infections and exposure to other chemicals, were inapplicable in this case and that Plaintiff's mother's multiple exposures to Benlate

[4] The District Court did not question the qualifications of Plaintiff's experts, and the Fourth Circuit Court of Appeals found them to be both "credible and qualified." (App. 2).

during the critical time period in the development of Plaintiff's embryonic eyes, caused his anophthalmia.[5]

The District Court excluded the testimony of Drs. Howard and Tackett, holding that their conclusions that benomyl is a human teratogen at certain levels, having been extrapolated from "high-dosage single species *in vivo* testing and lengthy benomyl exposure *in vitro* testing," were neither reliable nor relevant, where the only existing epidemiological evidence was contrary to Plaintiff's position. The District Court found that Plaintiff's experts' rejection of three epidemiological studies relating to pesticide exposure and birth defects, based upon their reliance upon the opinion of Dr. Ozonoff, Plaintiff's epidemiologist, was unjustifiable where Ozonoff himself erred in rejecting these studies. The Fourth Circuit affirmed, holding that "the District Court properly exercised its 'gatekeeper' function by focusing on the methodology employed by the experts rather than the conclusions they reached." (App. 7).

REASONS FOR GRANTING THE PETITION

The Fourth Circuit violated Federal Rules of Evidence, Rule 702 and the mandates of this Court in *Daubert* when it approved the District Court's holding that Plaintiff's experts utilized improper methodology when they

[5] "Differential diagnosis" is "a standard scientific technique of identifying the cause of a medical problem by eliminating the likely causes until the most probable one is isolated." *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 262 (4th Cir. 1999).

relied on an *unchallenged* expert epidemiologist who had discounted the significance and reliability of flawed studies DuPont claimed failed to establish epidemiological support for a finding of general causation. The egregiousness of this ruling is exacerbated where the District Court focused on and overruled the conclusions reached by the epidemiologist, rather than focusing on the methodology employed by Plaintiff's expert teratologist and pharmacologist.

"There are thousands upon thousands of synthetic agents being used in the United States that might pose toxic risks, yet only a tiny fraction have been the subject of any epidemiological inquiry."[6] Moreover, "[t]here is no perfect epidemiological study." *In re Phenylpropanolamine (PPA) Products Liability Litigation*, 289 F.Supp.2d 1230, 1240 (W.D.Wash. 2003). Not surprisingly, requiring positive epidemiology to prove causation is inconsistent with scientific practice. But in affirming the District Court's decision, the Fourth Circuit, contrary to the holding from several other circuits, implicitly overruled its own earlier decisions holding that epidemiological support was not a prerequisite to establishing causation in toxic tort cases. The question of whether *Daubert* requires positive epidemiology to support a finding of causation in a toxic tort case is an issue that has divided the Circuit Courts of Appeal. This division of authority among the circuits cannot be resolved absent this Court's intervention.

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[6] Michael D. Green, *Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of Agent Orange and Bendectin Litigation*, 86 Nw. U. L. Rev. 643, 680 n. 32.

I. In Upholding the Decision of the District Court, which Excluded the Testimony of Plaintiff's Expert Teratologist and Pharmacologist, in Large Part by Focusing on and Overruling the *Unchallenged* Conclusions of the *Unchallenged* Epidemiologist upon Whose Opinions Plaintiff's Experts Relied, Rather than Focusing on the Methodology Employed by Plaintiff's Experts, the Fourth Circuit Fundamentally Misinterpreted *Daubert* and FRE 702.

In support of its opposition to the testimony of Drs. Howard and Tackett, DuPont contended that three epidemiological studies, known as the Spagnolo, Kristenson and Dolk studies, failed to demonstrate an association between anophthalmia and exposure to Benlate. Plaintiff's expert epidemiologist, Dr. David Ozonoff, concluded that each study was so flawed as to render it incapable of providing reliable information on the existence of an association between maternal Benlate exposure and children's anophthalmia. Dr. Howard, a medical doctor and teratologist and Dr. Tackett, a toxicologist, relied upon Dr. Ozonoff's opinion in formulating their own expert opinions that maternal Benlate exposure had caused Plaintiff's injuries. DuPont did not attack Dr. Ozonoff's qualifications or conclusions, nor did DuPont seek to exclude his testimony. Indeed, epidemiology merited only four pages of discussion in DuPont's 126-page Motion to Exclude. Nonetheless, the principal reason the District Court excluded the testimony of Drs. Howard and Tackett was their reliance on Dr. Ozonoff's conclusion that these epidemiological studies were flawed and irrelevant.

The only question properly before the District Court was whether Drs. Howard and Tackett, by relying on the opinion of an expert epidemiologist, were "employ[ing] in

the courtroom the same level of intellectual rigor that characterizes the practice of an expert in [each expert's] relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999).

Here, Drs. Howard and Tackett were entitled to rely upon Dr. Ozonoff's opinion in evaluating epidemiological studies. It seems beyond doubt that scientists rely on other scientists outside their own expertise as a matter of common practice. When epidemiologists study the relationship between scarring of the lung and asbestos exposure in sheet-metal workers, for instance, they rely on radiologists to read x-rays of the studied population and to categorize them according to the level of scarring. *See, e.g.*, Irving J. Selikoff & Ruth Lilis, *Radiological Abnormalities Among Sheet-Metal Workers in the Construction Industry in the United States and Canada: Relationship to Asbestos Exposure*, 46 Arch. Envtl. Health 30, 32 (1991). Likewise, oncologists will rely on radiologists and pathologists in diagnosing and treating cancer. *See, e.g.*, Wilbur A. Franklin, *Diagnosis of Lung Cancer: Pathology of Invasive and Preinvasive Neoplasia,* 117 Chest 80S (2000) (reviewing importance of pathologic type of lung cancer to clinical outcomes).

The Rules of Evidence provide a liberal standard as to what may constitute the basis of an expert's opinion. An expert may testify as long as the information upon which he relies is the type generally relied upon by experts in the particular field. *See Fed. R. Evid.* 703; *Gussack Realty Co. v. Xerox*, 224 F.3d 85, 95 (2nd Cir. 2000) (Under Rule 702, an expert witness need not have conducted her own tests in order for her testimony to be admissible.); *Erickson v. Baxter Healthcare, Inc.*, 151 F.Supp.2d 952 (N.D.Ill. 2001) ("An expert witness may form opinions by studying or

observing the work of others rather than through first hand participation."); *Katt v. City of New York*, 151 F.Supp.2d 313, 356 (S.D.N.Y. 2001).

In the courtroom, testifying experts commonly rely on tests and published studies performed by other experts outside their field. To hold otherwise would require each expert to be qualified in a variety of fields, a holding that would turn the concept of an expert witness on its head. Rather than requiring that the witness be a specialist in whichever field a party proposes to propound his testimony, thus guaranteeing a particular expertise, the alternative would require the witness to be a jack-of-all-trades, thus guaranteeing no particular expertise. Here, neither Dr. Howard nor Dr. Tackett were presented as, or qualified as experts in epidemiology. Rather, they relied upon Dr. Ozonoff, a highly qualified epidemiologist, to examine and interpret the existing epidemiology regarding Benlate and anophthalmia.

The District Court, while paying lip service to *Daubert*, did not even limit itself to examining whether Dr. Ozonoff himself employed reliable methodology. Instead, the District Court compounded its error of looking beyond Drs. Howard and Tackett's methodology when it actually decided the merits of the question put to Dr. Ozonoff: whether the existing epidemiological studies were relevant to determining whether benomyl was a human teratogen. The District Court determined that Ozonoff was wrong to conclude that these studies were not helpful. *See Bourne v. E.I. DuPont De Nemours & Company, Inc.*, 189 F. Supp.2d 482, 493 (S.D.W.Va. 2002), ("Inasmuch, however, as Dr. Ozonoff acknowledged that the use of exposure surrogates, as in the Spagnolo study, is common in the field of epidemiology, and considering he provided only conclusory and

speculative remarks about the Kristenson study and the Dolk study, it appears that the blanket rejection by Drs. Howard and Tackett of these epidemiological studies was unfounded.")[7] *See also Id.*, at 497 ("The only existing

[7] The use of surrogates in epidemiology does not lessen the likelihood of misclassification. As Dr. Ozonoff testified: "A true individual-level analysis (not requiring cross-level inference) was also attempted by Spagnolo, *et al.* The 'non-cases' were actually another birth defect, pre-auricular tags thought unrelated to pesticide exposure. Cases or non-cases were classified for exposure by the parental occupation of agricultural worker. Such an exposure surrogate is likely to be highly misclassified (misclassifications of over 50% would not be unlikely), making any estimate of the effect strongly biased. No attempt to control for confounding was made, and the likely underascertainment noted by Kallen, *et al.* [underascertainment in the rates of conditions commonly described as anophthalmia and microphthalmia in birth defect registries] will produced a strong selection bias of unknown extent and direction. Moreover, even accepting the data as given, the confidence intervals are wide, indicating considerable imprecision in the estimate."

Dr. Ozonoff's criticisms of the Dolk and Kristenson studies were neither conclusory nor speculative. The Kristenson study used farm families as surrogates for exposure to pesticides in general and did not even mention Benlate or benomyl. Worse, neither microphthalmia nor anophthalmia, which Kristenson acknowledged are rare diseases, were specifically mentioned among the birth defects reported. P. Kristenson, *et al.*, *Birth Defects Among Offspring of Norwegian Farmers, Epidemiology* 8:537-44 (1997). Kristenson himself later noted in a letter to the British Medical Journal that "[I]ts [Benomyl's] use has been limited in Norway." According to Ozonoff, epidemiological studies are "worthless" where there are rare or uncommon exposures, such as in Norway, and rare outcomes, *i.e.*, anophthalmia.

The aforementioned Kallen paper specifically noted as much as 50% underascertainment of anophthalmia and microphthalmia in the British birth defect registry, the very registry utilized by Dolk. Dr. Ozonoff concluded that the Dolk study was uninformative with respect to its attempts to study clustering of anophthalmia, where clustering studies are notoriously insensitive to begin with. Dr. Ozonoff did find the Dolk study finding of *higher* anophthalmia risk in rural areas

(Continued on following page)

epidemiological evidence is contrary to plaintiff's position.") (footnote omitted).

As the Fourth Circuit acknowledges, Rule 702 of the Federal Rules of Evidence "was intended to liberalize the introduction of relevant expert evidence. . . . *Daubert* reminds us that, as with all other admissible evidence, expert evidence is subject to being tested by '[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof.'" (App. 6)

And while this Court in *Daubert* noted that expert witnesses have the potential to "be both powerful and quite misleading", *id.* at 595 (internal quotation marks omitted), that potential was non-existent in this case, where DuPont presented the testimony of *three* toxicologists, *three* teratologists and a plethora of other experts whose purpose was to explain away or dispute the human studies, animal studies, *in vitro* tests, regulatory classifications and other data upon which Plaintiff's experts relied. There was thus an abundance of "contrary evidence" to the evidence that Plaintiff sought to present. DuPont's overwhelming lead in the sheer number of experts would negate any concern that Plaintiff's experts were potentially "powerful and misleading." *Id.*

The inquiry that was to be undertaken by the District Court is "a flexible one" focusing on the "principles and

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"germane and somewhat informative," where the authors of that study assumed that persons living in rural areas were more likely to be exposed to benomyl. Dr. Ozonoff noted that (as with the Spagnolo study) there was "plenty of room for exposure misclassification." Here, however, such misclassification would tend to *underestimate* the risk of anophthalmia from exposure to benomyl.

methodology" employed by the expert, not on the conclusions reached. *Daubert* at 594-95. While "conclusions and methodology are not entirely distinct from one another" *General Elec. Co. v. Joiner,* 522 U.S. 136, 146 (1997), trial judges should err on the side of caution when exercising their gate keeping role in order to ensure against the improper conversion of an evidentiary determination into a determination on the issue of factual causation. *See*, Danielle Conway-Jones, *Factual Causation in Toxic Tort Litigation: A Philosophical View of Proof and Certainty in Uncertain Disciplines*, 35 U. Rich. L. Rev. 875, 921 (2002). Here, the District Court, in essence, excluded the testimony of Dr. Howard, a teratologist, and Dr. Tackett, a pharmacologist, by ambush. DuPont did not seek to exclude Dr. Ozonoff, Plaintiff's epidemiologist, yet the District Court used Ozonoff's analysis of the existing Benlate epidemiology as the primary basis to exclude Howard and Tackett's testimony. The District Court clearly abused its role as "gatekeeper" in substituting its opinion for the conclusions of a qualified expert whose testimony DuPont had not even sought to exclude.

II. The Fourth Circuit's Opinion, Upholding the Decision of the District Court Effectively Holding that an Expert Witness Cannot Provide Causation Testimony without Support from "Positive" Epidemiological Studies, Conflicts with Decisions of Other Courts of Appeal.

The District Court's decision requires that Plaintiff's experts provide "positive" epidemiological evidence to support their opinions on causation, especially where the available epidemiological data are inconclusive. After rejecting Dr. Ozonoff's opinion disputing the relevance

and reliability of the existing epidemiological studies purporting to address the link between Benlate and anophthalmia, the District Court stated that it was skeptical of Plaintiff's experts' reliance on rat gavage and *in vitro* tests in the absence of "epidemiological evidence supporting the proposition that benomyl is a human teratogen." *Bourne, supra*, 189 F. Supp.2d at 498 n. 23.

The Fourth Circuit's opinion, upholding the District Court's requirement of positive epidemiology to prove causation, is inconsistent even with that circuit's prior jurisprudence. The Fourth Circuit had previously recognized that epidemiological proof is helpful, but not necessary to support opinions on causation. *See Westberry v. Gislaved Gummi AB*, 178 F.3d 257 (4th Cir. 1999) (finding no abuse of discretion where expert relied on no epidemiological studies; no peer-reviewed published studies, no animal studies, and no laboratory data); *Benedi v. McNeil-P.P.C., Inc.*, 66 F.3d 1378 (4th Cir. 1995) ("[W]e do not read *Daubert* as restricting expert testimony to opinions that are based solely upon epidemiological data . . . as long as the methodology employed by the expert in reaching his or her conclusion is sound.").

The Fourth Circuit's opinion also conflicts with the opinions of other federal courts of appeal. *See, e.g., Kennedy v. Collagen Corp.*, 161 F.3d 1226 (9th Cir. 1998) (medical expert's opinion that collagen caused autoimmune disorders such as atypical systemic lupus erythematosus (SLE) suffered by plaintiff after collagen injections reflected "scientific knowledge," despite lack of epidemiological or animal studies); *Bonner v. ISP Technologies, Inc.*, 259 F.3d 924, 929 (8th Cir. 2001) ("[T]here is no requirement that published epidemiological studies supporting an expert's opinion exist in order for the opinion to be admissible.");

Turpin v. Merrell Dow Pharmaceuticals, Inc., 959 F.2d 1349, 1357 (6th Cir. 1992) (Rejecting the proposition that one can conclude that a drug is not teratogenic simply because epidemiology fails to establish a link or association. "[M]any of the defendant's studies apparently do not control for many factors that may be crucial for scientists to accord great weight to the studies, such as the stage of pregnancy during which the mother took Bendectin, the other drugs the mother may have taken, or other harmful conditions, natural or otherwise, that may have been part of the mother's environment. . . . The science of epidemiology is currently unable to identify the causes of many birth defects or to exclude from consideration many possible causes, including Bendectin and a host of other outside agents and environmental factors."); *Ambrosini v. Labaraque*, 101 F.3d 129, at 134, 138 (D.C. Cir. 1996), *cert. dismissed*, 520 U.S. 1205 (1997) ("A cause-effect relationship need not be clearly established by animal or epidemiological studies before a doctor can testify that, in his [or her] opinion, such a relationship exists. . . . [P]roducts liability law does not preclude recovery until a 'statistically significant' number of people have been injured, and that the fact that science would require more evidence before conclusively considering the causation question resolved is irrelevant." (quotations omitted).[8]

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[8] Some Circuit Courts of Appeal do appear to require positive epidemiological studies to demonstrate causation. *See, e.g., Brock v. Merrill-Dow Pharmaceuticals, Inc.*, 874 F.2d 307, 313 (5th Cir. 1989), *modified by*, 884 F.2d 166 (5th Cir. 1989), *cert. denied*, 494 U.S. 1046 (1990). ("We find, in this case, the lack of conclusive epidemiological proof to be fatal to the Brock's case. While we do not hold that epidemiologic proof is a necessary element in all toxic tort cases, it is certainly a

(Continued on following page)

Cases such as *Bonner* and *Ambrosini* are consistent with historical scientific practice, which traditionally relies on information from many different areas of inquiry – *in vivo* studies, case reports, molecular analyses and epidemiology – to evaluate etiologic relationships. Without question, epidemiology can be a powerful tool in assessing causation, especially for quantitatively evaluating population-based risks. It does not follow, however, that a scientist who concludes that the existing epidemiology is inconclusive is practicing unreliable science by relying on other data to evaluate causation. Indeed, many etiological relationships have been recognized in the absence of epidemiological data.

Indeed, in the field of teratology, reliance on non-epidemiological data may be more common than in other fields, because of how difficult it is to conduct epidemiological studies when the exposure is difficult to assess and the outcome is rare, as it is for most birth defects. *See* Jane Adams & Sherry G. Sclevan, *Issues and Approaches in Human Developmental Toxicology*, in Developmental Toxicology 28, 288 (C.A. Kimmel & J. Buelke-Sams eds., 1994) (noting that case-control studies are often used to study rare outcomes, but these studies still require "a relatively common exposure"). Thalidomide, a universally recognized human teratogen, was pulled from pharmacy shelves not because of epidemiological studies but because of case reports linking the drug to serious birth defects. *See* Max Sherman & Steven Strauss, *Thalidomide: A Twenty-Five Year Perspective*, 41 Food Drug Cosm. L.J. 458

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very important element."); *Lynch v. Merrell-Nat'l Labs.*, 830 F.2d 1190, 1194 (1st Cir. 1987).

(1986) (describing history of thalidomide disaster and noting that drug was pulled from market in Germany in same year that case reports of its teratogenic effects were published). *See also* M. Friedman & Janine E. Politka, *Teratogenic Effects of Drugs: A Resource for Clinicians*, 2d ed. (2000) ("Almost all exposures that are currently recognized as being teratogenic were initially identified in case reports and clinical studies. This is possible because teratogenic exposures typically produce qualitatively distinct patterns of congenital anomalies in affected children."). Even in other environmental exposure cases, such as asbestos, observant clinicians were among the first to observe health effects of asbestos exposure, well before epidemiological studies were published. *See* W.C. Hueper, *Occupational and Environmental*, 25 Bull. Am. Soc. Control Cancer 63 (1943); Richard Doll, *Mortality from Lung Cancer in Asbestos Workers*, 2 Brit. J. Ind. Med. 81 (1995) (first epidemiological study of asbestos exposure and lung cancer).[9] Further, to take an example from preventative medicine, the connection between fluoridated water and reduced tooth decay was first suggested by a clinician's observations, decades before epidemiology provided evidence of the relationship. *See* David E. Lilienfeld & Paul D. Stolley, *Foundations of Epidemiology* 5-6 (3d ed. 1994).

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[9] An association between disease and drug use is of course much easier to study than an association between disease and chemical exposure. Asbestos may be the biggest exception to this particular rule of thumb. Benlate exposure to women three to eight weeks pregnant, is exceedingly rare, whereas millions of workers have been exposed to asbestos.

Thus, the holding below that "reliable" teratologists require supportive epidemiology before concluding that a particular substance caused a birth defect cannot be reconciled with scientific practice. While it might be that scientists are unable to make quantitative estimates of the "strength and statistical significance" of causal associations absent epidemiological evidence, that does not mean that, absent epidemiology, a doctor cannot conclude that a substance is, within a reasonable degree of medical certainty, a human teratogen. Courts properly recognize the insight that epidemiology offers scientists in assessing causation, but the Fourth Circuit strayed when it imposed criteria that are not followed by the medical and scientific community, thereby giving epidemiology greater weight in assessing legal causation than scientists give it. This is particularly troubling given that numerous problems common to epidemiological studies, such as those articulated by Dr. Ozonoff, make them inconclusive. *See* Heidi Feldman, *Science and Uncertainty in Mass Exposure Litigation*, 74 Tex. L. Rev. 1, 24 (1995).

Not only has the Fourth Circuit previously recognized that epidemiological proof is not necessary to support opinions on causation, *see Westberry, supra*, that Circuit has long acknowledged that Rule 702 of the Federal Rules of Evidence "was intended to liberalize the introduction of relevant expert evidence." *Bourne v. E.I. DuPont De Nemours & Company, Inc.*, *supra*, 85 Fed.Appx. 964, 2004 WL 117634 (4th Cir. 2004) (citing cases). In *Daubert*, this Court rejected the argument that the "general acceptance" test articulated in *Frye v. United States*, 293 F. 1013 (D.C. Cir. 1923), should govern the admissibility analysis. Instead, this Court concluded that the "rigid general acceptance requirement would be at odds with the liberal

thrust of the Federal Rules and their general approach of relaxing the traditional barriers to 'opinion' testimony." *Daubert*, 509 U.S. at 587.

As certain commentators have observed, however, the discretion granted trial courts has continued to widen as the gate keeping function has evolved from *Daubert* through *Kumho Tire*, *supra*, including the discretion regarding which factors to consider in evaluating the reliability of particular expertise – substantive discretion – and discretion regarding their ultimate decisions on admissibility – decisional discretion – has led to some curious and unwanted results. *See*, *Note: Reliable Evaluation of Expert Testimony*, 116 Harv. L. Rev. 2141 (2003).

As the Tenth Circuit observed in *Hollander v. Sandoz Pharmaceuticals, Corp.*, 289 F.3d 1193, 1205-06 (10th Cir. 2002):

> Because the district court has discretion to consider a variety of factors in assessing reliability under *Daubert,* and because, in light of that discretion, there is not an extensive body of appellate case law defining the criteria for assessing scientific reliability, we are limited to determining whether the district court's application of the *Daubert* [sic] manifests a clear error of judgment or exceeds the bounds of permissible choice in the circumstances. . . . Thus, when coupled with this deferential standard of review, *Daubert's* effort to safeguard the reliability of science in the courtroom may produce a counter-intuitive effect: different courts relying on the essentially the same science may reach different results. [sic] *See generally Federal Judicial Center, Reference Manual on Scientific Evidence* 27 (2d ed.2000) (observing that, in light of the abuse of discretion standard

> of review for *Daubert* determinations of reliability, "in theory judges are free to select different procedures and apply different factors to a particular expert or type of expertise than their colleagues do in the same district or circuit" and that "[a]s a consequence, similar cases could be resolved differently on the basis of inconsistent determinations about admissibility").

Indeed, Dr. Howard's opinion that benomyl is a human teratogen and the scientific method underlying this entire litigation has generated two entirely disparate decisions. On the one hand is *Bourne*, resulting in the exclusion of Dr. Howard's testimony under the *Daubert* standard. On the other is *Castillo v. E.I. Du Pont De Nemours & Co., Inc.*, 854 So.2d 1264 (Fla.2003), decided by the Florida Supreme Court under the more restrictive *Frye* standard while the instant case was on appeal to the Fourth Circuit.

In *Castillo*, Dr. Howard testified that fetal exposure to benomyl at the concentration of 20 parts per billion (ppb) in the maternal bloodstream would cause microphthalmia in humans based on his conclusions from (1) rat gavage studies, (2) lab experiments on human and rat cells and (3) the results of dermal exposure testing done by DuPont's own scientists. He testified that he relied upon an expert epidemiologist who had considered and rejected the Dolk, Kristenson and Spagnolo epidemiological studies as flawed. In reviewing Dr. Howard's consideration of epidemiology under the *Frye* standard, the Florida Supreme Court stated:

> While epidemiology is considered generally accepted in the scientific community as a way of studying causal links between disease and

> chemicals, these types of studies are not necessarily required for a party to meet its burden of showing the causal link by a preponderance of the evidence. (Citing cases). In any event, the Castillos' experts did consider epidemiological studies. However, the parties disagree about the conclusions those epidemiological studies reached.
>
> It is clear that the Castillos do not need to present epidemiological studies to meet their burden. It is also clear that there were at least three studies at the time of the *Frye* hearing that the Castillos' experts considered and then deemed inconclusive to establish a causal link between benomyl exposure and microphthalmia, or lack thereof. DuPont and Pine Island's objections are to the conclusions the Castillos' experts reached, not the methodology itself. The Castillos' experts did indeed consider epidemiological studies, and the consideration of the studies in light of the parties' assertions as to their effect was properly put to the jury.

Castillo, 854 So.2d at 1270.

Thus, the Florida Supreme Court affirmed the admission of Dr. Howard's testimony even though crucial factors underlying his opinion, including DuPont's rat gavage study demonstrating that benomyl concentrates in the uveal tract of the eye, where it has an extended half-life, and *in vivo* studies on volunteers demonstrating the transdermal assimilation and consequent bioavailability of benomyl and MBC, had not yet been performed and therefore were not available for his consideration.

Cases such as this cry out for intervention by this Court, so that the district courts, in exercising their

discretion, will have sufficient guidance in their application of Rule 702, thus promoting uniformity of federal evidentiary standards. *See United States v. Bynum*, 362 F.3d 573, 584 (9th Cir. 2004).

CONCLUSION

Because the Fourth Circuit's holding violates this Court's mandate in *Daubert*, and because it reveals a split among the circuits regarding the necessity of positive epidemiology in toxic tort cases, this Court should grant the Petition for a Writ of Certiorari.

Respectfully submitted,

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This case was not selected for publication in the Federal Reporter.

UNPUBLISHED

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United States Court of Appeals,
Fourth Circuit

Andrew BOURNE, a minor by and through his parents, next friends and natural guardians, Chris BOURNE and Maggie Bourne, Plaintiff-Appellant, v. E.I. DUPONT DE NEMOURS & COMPANY, d/b/a DuPont, a Foreign Corporation, Defendant-Appellee. Trial Lawyers for Public Justice, Amicus Curiae.

No. 02-1469.

Argued Oct. 29, 2003.
Decided Jan. 27, 2004.

Appeal from the United States District Court for the Southern District of West Virginia, at Charleston. John T. Copenhaver, Jr., District Judge. (CA-97-90-2).

ARGUED: James Louis Ferraro, Ferraro & Associates, P.A., Miami, Florida, for Appellant. Patrick William Lee, Crowell & Moring, L.L.P., Washington, D.C., for Appellee. **ON BRIEF:** Scott S. Segal, The Segal Law Firm, Charleston, West Virginia, for Appellant. William L. Anderson, Emma K. Burton, Crowell & Moring, L.L.P., Washington, D.C.; David B. Thomas, Allen, Guthrie & McHugh, Charleston, West Virginia, for Appellee. Arthur

Bryant, Trial Lawyers for Public Justice, Oakland, California; Alexander A. Reinert, Koob & Magoolaghan, New York, New York, for Amicus Curiae.

Before WIDENER, *NIEMEYER* and *GREGORY*, Circuit Judges.

Affirmed by unpublished PER CURIAM opinion.

Unpublished opinions are not binding precedent in this circuit. See Local Rule 36(c).

OPINION

PER CURIAM.

I.

Plaintiff Andrew Bourne ("Bourne"), a minor, is suing the manufacturer of a pesticide called "benlate" (active ingredient is "benomyl"), which he alleges caused his teratogenic birth defects. In the district court, Bourne offered expert evidence from two credible and qualified experts to establish both specific and general causation. The district court, however, excluded the testimony of Bourne's experts finding it unreliable under *Daubert* and Rule 702 of the Federal Rules of Evidence. After excluding Bourne's only expert testimony on causation, the district court granted E.I. DUPONT DE NEMOURS AND COMPANY, INC.'s, ("DuPont"), motion for summary judgment and dismissed the case. We AFFIRM.

II.

Bourne by and through his parents, Christopher Bourne ("Mr. Bourne") and Maggie Bourne ("Mrs.

Bourne"), all residents of Essex, England, filed this action in February of 1997 against DuPont alleging that Mrs. Bourne's exposure to the DuPont-manufactured agricultural fungicide Benlate, while pregnant with Bourne, caused him to be born with severe birth defects.

Mrs. Bourne contends that she purchased Benlate from a local nursery to use in her home garden in March of 1986. The Benlate was packaged in small sachets roughly the size of an individual-serving sugar packet. Each sachet contained 2.25 grams of Benlate powder, approximately 53% of which was comprised of Benlate's active ingredient, the chemical benomyl. Also supplied with the Benlate were separate sachets containing 3.0 grams of a surfactant (surface active substance) called "Activex." According to the directions contained in the package of Benlate, each sachet of Benlate powder was to be mixed with a sachet of Activex along with one UK gallon of water (approximately 4.5 liters) before application to plants.

Mrs. Bourne contends that she followed the instructions and mixed a sachet of the Benlate and a sachet of the Activex in a gallon of water. Mrs. Bourne says that she sprayed the entire gallon of the Benlate-Activex-water mixture (hereinafter "Benlate mixture") on her home garden every ten to twelve days from March through late-June, 1986. She testified at her deposition that she applied the Benlate mixture liberally to her beans, strawberries, and roses, using a watering can, and when the beans grew taller, using both a watering can and a hand sprayer. She testified that it took her approximately 45 minutes-to-one-hour to mix and apply the Benlate mixture to her plants.

Mrs. Bourne wore no gloves or protective face covering while working with the Benlate. She testified that some

Benlate powder got on her hands when she prepared the Benlate mixture and that the Benlate mixture got on her hands and perhaps her legs as she stirred the Benlate mixture. She further testified that when she applied the Benlate mixture to her plants, the solution would get on her hands, legs, feet, and possibly her face. She bathed every day or every other day.

Mrs. Bourne became pregnant with Bourne on or about May 5, 1986. The child was born on January 27, 1987, with bilateral clinical anophthalmia (the complete absence of eyes), hypogonadatropic hypogonadism (a pituitary disorder resulting in this case in small stature and underdeveloped genitalia), and mental retardation. Bourne contends that his mother's repeated exposure to Benlate during critical periods in his fetal development caused or contributed to his birth defects.

III.

This court reviews the decision of a district court to admit or exclude evidence for abuse of discretion. *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 261 (4th Cir.1999) (citing *General Elec. Co. v. Joiner*, 522 U.S. 136, 139, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)). A district court abuses its discretion if its conclusion is guided by erroneous legal principles, *see id.* (citing *Koon v. United States*, 518 U.S. 81, 100, 116 S.Ct. 2035, 135 L.Ed.2d 392 (1996)), or rests upon a clearly erroneous factual finding. *United States v. Barber*, 119 F.3d 276, 283 (4th Cir.1997) (*en banc*). Further, even if a district court applies the correct legal principles to adequately supported facts, the discretion of the trial court is not boundless and subject to automatic affirmance. *Westberry*, *supra*, (citation omitted).

This court is obliged to review the record and reasons offered by the district court and to reverse only if the "court has a definite and firm conviction that the court below committed a clear error of judgment in the conclusion it reached upon a weighing of the relevant factors." *Id.*

IV.

The introduction of expert opinion testimony is governed by Federal Rule of Evidence 702, which provides, in pertinent part:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert . . . may testify thereto in the form of an opinion or otherwise.

FED. R. EVID. 702 (West 2002).

Expert testimony is admissible under Rule 702, then, if it concerns (1) scientific, technical, or other specialized knowledge that (2) will aid the jury or other trier of fact to understand or resolve a fact at issue. *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 592, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). The first prong of this inquiry necessitates an examination of whether the reasoning or methodology underlying the expert's proffered opinion is reliable – that is, whether it is supported by adequate validation to render it trustworthy. *Westberry*, 178 F.3d at 261 (citing *Daubert*, 509 U.S. at 590). The focus of the first prong is therefore on the issue of reliability. The second prong of the inquiry requires an analysis of whether the opinion is relevant to the facts at issue. *Id.* (citing *Daubert*, 509 U.S.

at 591-92). The focus of the second prong has, thus, been described as "fit."

Ultimately, an expert's testimony is admissible under *Rule 702* if it "rests on a reliable foundation and is relevant." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 141, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999) (internal quotation marks omitted). The district court's role in considering the admissibility of expert testimony is that of a "gate-keeper" whose prime task is to assess whether the proffered evidence is sufficiently reliable and relevant. *See id.* at 1174. As the gate-keeper, the district court's inquiry is "a flexible one" focusing on the "principles and methodology" employed by the expert, not on the conclusions reached. *Daubert*, 509 U.S. at 594-95 (emphasis added). In making its initial determination of whether proffered testimony is sufficiently reliable, the court has broad latitude to consider whatever factors bearing on validity that the court finds to be useful; the particular factors will, however, depend upon the unique circumstances of the expert testimony involved. *Kumho Tire Co.*, 526 U.S. at 149-50.

As the gate-keeper, the court must remain conscious of two guiding, and sometimes competing, principles. *Westberry*, 178 F.3d at 261. On the one hand, the court should be mindful that Rule 702 was intended to liberalize the introduction of relevant expert evidence. *Id.* (citing *Cavallo v. Star Enter.*, 100 F.3d 1150, 1158-59 (4th Cir.1996)). Thus, the court need not determine that the expert's proffer is irrefutable or certainly correct. *Id.* In liberalizing the standard for admission, *Daubert* reminds us that, as with all other admissible evidence, expert testimony is subject to being tested by "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof." *Daubert*, 509

U.S. at 596. On the other hand, *Daubert* cautions that the district court must recognize that due to the difficulty of evaluating their testimony, expert witnesses have the potential to "be both powerful and quite misleading." *Id.* at 595 (internal quotation marks omitted). Where the expert proffer has a greater potential to mislead than to enlighten, that evidence may properly be excluded. *Westberry* (citing *United States v. Dorsey*, 45 F.3d 809, 815-16 (4th Cir.1995)).

V.

The district court's well-reasoned opinion properly balances the two guiding, and sometimes competing, principles underlying the *Daubert* analysis. *Westberry*, 178 F.3d at 261. When excluding the proffered testimony, the district court properly exercised its "gate-keeper" function by focusing on the methodology employed by the experts rather than the conclusions they reached. *Daubert*, 509 U.S. at 594-95. Thus, we can not say that the district court abused its discretion. On the reasoning stated by the district court, as reported at *Bourne v. E.I. Dupont de Nemours & Company, Inc.*, 189 F.Supp.2d 482 (S.D.W.Va.2002), we therefore AFFIRM.

AFFIRMED.

189 F.Supp.2d 482

United States District Court, S.D. West Virginia.

Andrew BOURNE, a minor by and through his Parents, next friends and natural guardians, Chris BOURNE and Maggie Bourne, Plaintiff

v.

E.I. DUPONT DE NEMOURS AND COMPANY, INC., Defendant

No. CIV A 2:97-0090.

March 29, 2002.

James L. Ferraro, Lynn M. Holtzman, Markenzy Lapointe, Diana L. Rolfs, Ferraro & Associates, P.A., Miami, FL, Scott S. Segal, The Segal Law Firm, Charleston, WV, for Plaintiff.

Patrick W. Lee, William L. Anderson, Emma K. Burton, Crowell & Moring, LLP, Washington, DC, David B. Thomas, Philip J. Combs, Allen, Huthrie & McHugh, Charleston, WV, for Defendant.

MEMORANDUM ORDER[1]

COPENHAVER, District Judge.

This matter is before the court on the motion of defendant E.I. DuPont De Nemours and Company, Inc.

[1] Following the issuance of the court's memorandum order of January 11, 2002, counsel for the plaintiff requested that the evidentiary deposition of Dr. David M. Ozonoff taken December 17, 2001, be made a part of the record in this case, to which the defendant had no objection. The court has seen fit to withdraw its memorandum order of January 11, 2002, in order that the section on epidemiology there set forth on pages 20 through 24 may take into account Dr. Ozonoff's testimony at his evidentiary deposition.

("DuPont") to exclude the testimony of Dr. Charles Vyvyan Howard and Dr. Randall L. Tackett, plaintiff's causation experts in the above-styled toxic tort action, filed December 5, 2001. Inasmuch as plaintiff's principal expert, Dr. Howard, has been extensively deposed on multiple occasions and Dr. Tackett has also been deposed and inasmuch further as the motion has been the subject of extensive submissions by both parties, the court concludes and the parties agree that the record is complete and a hearing on the motion is not needed.

I.

Minor plaintiff Andrew Bourne ("Bourne") by and through his parents, Christopher Bourne ("Mr.Bourne") and Maggie Bourne ("Mrs.Bourne"), all residents of Essex, England, filed this action in February of 1997 against DuPont alleging that Mrs. Bourne's exposure to the DuPont-manufactured agricultural fungicide Benlate, while pregnant with the plaintiff, caused plaintiff to be born with severe birth defects.[2]

Mrs. Bourne contends that she purchased Benlate from a local nursery to use in her home garden in March of 1986. (Mrs. Bourne Dep. at 39-41.) The Benlate was

[2] During the pendency of this case, as will be more fully noted, the parties have engaged in studies of Benlate's active ingredient, benomyl, and any relationship it may have to plaintiff's anophthalmia (the complete absence of eyes). The defendant completed and made available a pharmacokinetic study in early 1999. To rebut that study, the plaintiff was then allowed the time required to undertake a human dermal absorption study ("TNO study") that was completed in June, 2000. Plaintiff was permitted still further time to pursue a follow-up to that study that was completed in March, 2001.

packaged in small sachets roughly the size of an individual-serving sugar packet, with each sachet containing 2.25 grams of Benlate powder, approximately 53% of which was comprised of Benlate's active ingredient, the chemical benomyl. (Upstone Aff. at 5.) Also supplied with the Benlate were separate sachets containing 3.0 grams of a surfactant called "Activex." (*Id.*) According to the directions contained in the package of Benlate, each sachet of Benlate powder was to be mixed with a sachet of Activex along with one UK gallon of water, approximately 4.5 liters, before application on plants. (*See* copy of Benlate label, attached as Ex. C to Upstone Aff.)

Mrs. Bourne contends that she followed the instructions and mixed a sachet of the Benlate and a sachet of the Activex in a gallon of water. Mrs. Bourne says that she sprayed the entire gallon of the Benlate-Activex-water mixture (hereinafter "Benlate mixture") on her home garden every ten to twelve days from March through late June, 1986. (Mrs. Bourne Dep. 39, 45-47, 68.) She testified at deposition that she applied the Benlate mixture liberally to her beans, strawberries, and roses, using a watering can, and when the beans grew taller, using both a watering can and a hand sprayer. (*Id.* at 38-40, 43-46, 91.) She testified that it took her approximately 45 minutes to one hour to mix and apply the Benlate mixture to her plants. (*Id.* at 105.)

Mrs. Bourne wore no gloves or protective face covering while working with the Benlate. (*Id.* at 98-100.) She testified that some Benlate powder got on her hands when she prepared the Benlate mixture and that the Benlate mixture got on her hands and perhaps her legs as she mixed. (*Id.* at 84-85.) When applying the Benlate mixture to her plants, she testified that the solution would get on

her hands, legs, feet, and possibly face. (*Id.* at 85, 92-94, 96-97, 109.) She would bathe every day or every other day. (*Id.* at 128.)

Mrs. Bourne became pregnant with the plaintiff on or about May 5, 1986. (Ravits Dep. at 5-6.) The child was born on January 27, 1987, with bilateral clinical anophthalmia (the complete absence of eyes), hypogonadatropic hypogonadism (a pituitary disorder resulting in this case in small stature and underdeveloped genitalia), and mental retardation. (Mrs. Bourne Dep. at 128.) It is plaintiff's contention that his mother's repeated exposure to Benlate during critical periods in his fetal development led to his birth defects. (Pl.'s Compl. at ¶ 39.)

II.

In a toxic tort case, a plaintiff must generally establish both general and specific causation for his injuries. Bourne must establish that he, via his pregnant mother, was exposed to a human teratogen, both at a level and by a means capable of causing his birth defects. He must also establish that the exposure to the teratogen did, in fact, bring about his particular maladies. Drs. Howard and Tackett both opine that Mrs. Bourne was exposed to Benlate, which they contend to be a human teratogen, at a critical stage in her son's fetal development, with the Benlate being absorbed into her blood stream at a level capable of causing Bourne's defects. They rule out genetic causes for Bourne's birth defects, and each opines that Mrs. Bourne's Benlate exposure is more likely than not the cause of her son's anophthalmia. In their reports, neither Dr. Howard nor Dr. Tackett refers to the cause of the plaintiff's birth defects other than the anophthalmia.

Dr. Howard is the senior lecturer at the University of Liverpool in the Faculty of Medicine. He is a licensed medical practitioner and a fetal toxio-pathologist. According to his report, in reaching his conclusions, Dr. Howard relied upon various studies and reports involving Benlate, the deposition transcripts of the Bournes, reports of plaintiff's expert witnesses and plaintiff's physicians, the existing epidemiology studies[3] on Benlate, the United States Environmental Protection Agency ("EPA") and the European Community's classification of benomyl, his personal knowledge and experience, and "information previously identified in [his] deposition in this case and those taken in *Castillo.*" (*Id.* at 1.)

Dr. Tackett is a pharmacologist and a professor of pharmacology and Toxicology at the University of Georgia. Dr. Tackett reached the same conclusion as Dr. Howard with respect to the causation of Bourne's anophthalmia. His opinion is based upon "(1) the known pharmacological/toxicological actions of Benlate which have been demonstrated to produce anophthalmia; (2) exposure to Benlate at a critical time in Mrs. Bourne's pregnancy; and (3) the fact that dermal absorption of Benlate results in systematic levels of benomyl and its metabolites in humans." (Tackett report at 1.)

A. *Mrs. Bourne's exposure to Benlate*

Dr. Howard estimated the amount of Benlate to which Mrs. Bourne was dermally exposed, and Dr. Tackett

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[3] Epidemiological studies examine the pattern of disease in human populations.

adopted the estimate. Based upon Mrs. Bourne's deposition transcript, Dr. Howard opined that 30% of Mrs. Bourne's skin was exposed to 5% of the gallon of Benlate mixture each time she applied the Benlate to her plants every 10 to 12 days. The 5% figure, Dr. Howard testified, represents "how much liquid . . . [is necessary] to achieve the level of wetness which [Mrs. Bourne] described in her deposition." (Howard Dep. at 255.)[4] He also testified, however, that he engaged in back-calculation to arrive at the 5% figure, stating that the 5% is an "estimate of the volume of Benlate mixture in a one gallon can that would need to be splashed onto Mrs. Bourne to achieve 20 percent per billion[5] of benomyl equally distributed throughout her body with a dermal transmission rate of 3.5 percent of the dose." (*Id.* at 117.)

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[4] While Dr. Howard was deposed on a number of occasions, the deposition transcript representing the first 5 dates on which he was deposed appear on consecutively numbered pages. References to these first 5 dates (October 30, 1998; October 31, 1998; December 10, 1998; December 11, 1998; and April 30, 1998.) will hereinafter be referred to as "Howard Dep. at . . . " Dr. Howard's most recent deposition was taken on October 4, 2001, and the transcript of the deposition begins anew with page number 1. References to the October 4, 2001, deposition transcript will be designated by date and page.

[5] He likely intended to say "parts per billion" rather than "percentage per billion," with 20 parts per billion being the minimum concentration of benomyl which several *in vitro* studies found to be the lowest effect level for cells dosed with benomyl. *See infra* III.C. Dr. Howard has adopted the EPA-utilized 3.5% dermal absorption rate for benomyl through human skin.

The 5% of a gallon, which is 225 milliliters,[6] or 225,000 microliters, was spread, Dr. Howard opines, over 30% of Mrs. Bourne's body. (*Id.* at 331.) Mrs. Bourne's body surface area, based upon her height and weight, is found by him to be 15,000 square centimeters, with 30% thereof being 4,500 square centimeters. (*Id.* at 332.) Dr. Howard opines that Mrs. Bourne's dermal exposure to Benlate mixture was 50 microliters per square centimeter, or 12.5 micrograms of benomyl per square centimeter. (*Id.* at 332-333.)[7]

Dr. Howard admits that these figures are not measured values, but are estimates based upon Mrs. Bourne's deposition testimony. (*Id.* at 333-334.) Dr. Howard conducted no testing or measurements to arrive at his figures. (*Id.* at 255, 295, 331-34, 670-71.) He is unsure how much, if any, of the purported 50 microliters per square centimeter of the Benlate mixture either ran off of Mrs. Bourne's skin or was rubbed off onto her clothing. (*Id.* at 337-38.) He did not address a published study conducted by DuPont examining dermal exposure to Benlate in a home garden setting which concluded that dermal exposure to benomyl using two gallons of Benlate containing approximately 9.5 grams of benomyl in a compression sprayer was

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[6] In his deposition, he estimated a UK gallon to be at 4500 milliliters, leading to the 225 figure. A UK gallon is actually 4546.09 milliliters, with 5% thereof being 227.3.

[7] It appears that Dr. Howard used primarily volume measures in his depositions and metric weight measurers in his report. Using metric weight, Dr. Howard concluded that the weight of 5% of the benomyl present in the UK gallon was 56.25 milligrams, with a total amount deposited per square centimeter on Mrs. Bourne's skin at 10,000 nanograms. (Howard report at 3.)

less than 1 milligram of benomyl. *See* Leighton P. Everhart & Richard F. Holt, *Potential Benlate Fungicide Exposure During Mixer' Loader Operations, Crop Harvest, and Home Use,* 30 J. Agric. Food Chem. 222 (1982) ("DuPont Everhart study"). Converting 1 milligrams [sic] to 1,000 micrograms and dividing by 4,500, the number of square centimeters of Mrs. Bourne's body Dr. Howard contends was exposed to the Benlate mixture, then dividing by 2 to account for the study's use of 2 gallons, one is left with a figure of .11 micrograms per square centimeter. Dr. Howard's estimate of 12.5 micrograms per square centimeter exceeds this figure by about 113 times. (Howard Dep. at 333.) Nor did he address a study conducted by the National Institute for Occupational Safety and Health ("NIOSH") which found that nursery workers engaged in weighing, mixing, and applying Benlate with compression sprayers are exposed to between .14 and .19 micrograms of Benlate per square centimeter per hour on the thigh and lower leg. Hoekstra, Kiefer, and Tepper, *Monitoring of Exposure to Benomyl in Nursery Workers,* 38:8 J. Occup. Environ. Med. 775,779 (1996) ("NIOSH Hoekstra study") Dr. Howard's estimate of 12.5 micrograms per square centimeter would exceed the range found in that article by 66 to 89 times. Aside from a failure to address at least the NIOSH study, Dr. Howard points to no study supporting his calculation.

B. *Dermal Absorption*

The estimate of the dermal transmission rate of benomyl into human blood varies based upon the source. DuPont's expert, Dr. Howard I. Maibach, opines that the human dermal absorption rate for benomyl is less than 1%, whereas the United States Environmental Protection

Agency ("EPA") has adopted a 3.5% dermal transmission rate and the California EPA refers to a 10% dermal transmission rate.[8]

The dermal absorption rates of both the EPA and the California EPA are based upon rat studies. The EPA's figure is based upon a study conducted in 1978-79 by Belasco involving the dermal absorption of benomyl on rat skin. In this study, the dermal absorption rate was 3.5% after 10 hours at a .1 milligram dose, but with lower absorption rates for lesser time intervals.[9] The study found that the dermal absorption rate decreased as the doses of benomyl applied to the skin increased. (Ex. 29-30, Def.'s Mot. Exclude.) The California EPA's dermal absorption rate appears in a 1999 document entitled Benomyl (Benlate) Risk Characterization Document. The document states that it "assumes" a 10% dermal absorption rate based upon another California EPA report prepared in

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[8] Based upon the court's review of documents generated by the EPA's Hazard Identification Assessment Review Committee, on behalf of the Office of Pollution Prevention: Pesticides and Toxic Substances, the 3.5% dermal absorption rate and the referenced dermal dosage levels of benomyl appear to be utilized by the EPA merely for "the risk assessment for benomyl, and its primary metabolite carbendazim [MBC]." It does not appear that the EPA has made determinations about benomyl and its causation of teratogenic effects in humans. *See* Memorandum dated March 20, 2001, from Deborah Smegal, Toxicologist, entitled, "Benomyl and Carbendazim-Endpoint Selection for Incidental Oral Ingestion for Carbendazim."

[9] In the Belasco study, the dermal absorption level after 4 hours was 1.7% at a .1 milligram dose, .3% at a 1 milligram dose, .04% at a 10 milligram dose, and .03% at a 100 mg dose. After 10 hours of dermal exposure, the amount absorbed was 3.5% at a .1 milligram dose, .5% at a 1 milligram dose, and .09% at a 10 milligram dose, and .03% at a 100 milligram dose.

1998, entitled *Estimation of Exposure to Persons in California to Pesticide Products that Contain Benomyl,* by David Haskell and Louise Mehler. The 1998 report, referring to the Belasco rat study, utilizes a 10% dermal absorption rate. (Ex. 27-28, Def.'s Mot. Exclude.)

Based upon his estimation that Mrs. Bourne was dermally exposed to 56.25 milligrams of Benlate with each use, Dr. Howard calculated Mrs. Bourne's total amount of benomyl absorption using several different dermal absorption rates.[10] With a 5% transmission rate, 500 nanograms per square centimeter would be absorbed; with a 3.3% transmission rate, 330 nanograms per square centimeter would be absorbed, and with a 2% transmission rate, 200 nanograms per square centimeter would be absorbed. (Howard report at 2.) Assuming Mrs. Bourne has a blood volume of 4 liters, and converting nanograms to milligrams and then dividing by one million, Dr. Howard concluded that the amount of benomyl absorbed by Mrs. Bourne was 562, 375, or 225 parts per billion, with 5%, 3.3%, and 2% dermal absorption rates, respectively. (Howard Dep. at 361-62.) DuPont contends that there is no reliable evidence underlying Dr. Howard's use of these dermal absorption figures inasmuch as they are based solely on rat studies. Indeed, DuPont points out, plaintiff's own benomyl dermal absorption study, referred to below, lends no support to Dr. Howard's contention. It appears to be the only such study of living humans.

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[10] He testified at deposition that the "rate" is in "a non-temporal context." (Howard Dep. at 119.)

Plaintiff nevertheless asserts that in addition to the California EPA rat dermal absorption study finding a 10% dermal absorption, a study conducted for plaintiffs by TNO ("TNO study") in the Netherlands and led by W. Mueling, involving human dermal absorption of benomyl, provides "compelling evidence" of a dermal transmission rate of at least 3.5%. (Pl.'s Resp. Motion to Exclude Howard and Tackett at 28.) Drs. Howard and Tackett address the TNO study generally in their reports to state that the study provides evidence that benomyl applied dermally becomes bioavailable.[11] In the TNO study, the skin of eight adult human volunteers was dosed with 60 milligrams of Benlate solution, containing approximately 30 milligrams of benomyl, on both upper thighs for a four hour period. The blood of the test subjects was collected via canula for 6 hours following exposure, with the urine of the subjects collected for 72 hours following exposure. (TNO study at 3, attached as exhibit 36, Def.'s Motion to Exclude.) Urine and blood samples were also taken prior to Benlate administration. (*Id.*)

The study was conducted in two phases. In the first phase, the samples were analyzed by high performance liquid chromatography ("HPLC") to detect and measure benomyl metabolites MBC, 5-HBC, and STB. (Mueling Dep. at 74-76.) MBC is the only benomyl metabolite that Drs. Howard and Tackett believe to be teratogenic. (Howard Dep. at 240, 401-02; Howard 10/04/01 Dep. at 97-98;

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[11] Bioavailability is a term used to indicate the extent to which a chemical reaches tissues or bodily fluids, such as blood plasma, and is available to be transported throughout the body.

Tackett Dep. at 59.) Specifically, 5-HCB is not claimed by Drs. Howard and Tackett to be teratogenic. (*Id.*)

No MBC or STB was detected in any blood sample and only 1 of 176 blood samples had a detectable, but non-quantifiable, level (i.e., a trace) of 5-HBC. (TNO study at 3.) 5-HBC was detected and measured in the urine samples. (*Id.*) In the second phase of the test, half of the blood and urine samples were re-analysed using a more sensitive detection method called liquid chromatography-tandem mass spectrometry. (Mueling Dep. at 74-76.) MBC was detected in some plasma samples but not at quantifiable levels. (*Id.*) Again there were detectable amounts of the benomyl metabolite 5-HBC found in the urine excreted for up to 72 hours following exposure.

However, the highest levels of MBC detection were found in blood plasma samples taken prior to benomyl administration, and urine samples from four of the testing subjects tested positive for 5-HBC prior to any benomyl administration. (TNO study, Appendix 3) Mueling "speculate[s]" that the pre-dose benomyl metabolite detection could be the result of food ingested by the test subjects prior to the commencement of the study. (Mueling Dep. at 59-60.) Mueling testified that he only subtracted pre-exposure amounts of 5-HBC found in the urine and MBC found in plasma from the amounts of these metabolites found post-exposure when the pre-exposure amounts were deemed to be "significant." (*Id.* at 73-76.) On some test subjects, the amount of 5-HBC found pre-exposure was subtracted from the post-exposure amount, and on others it was not. (*Id.*) No amounts of pre-exposure MBC in plasma were subtracted from post-exposure MBC amounts. (*Id.*)

Mueling testified that no conclusions could be drawn from the second portion of the study and that other than listing those results in the TNO study report, he did not use the results for any other purpose. (*Id.* at 75-77.) The first portion of the study found "the plasma levels did not reach the limit of detection [and] [w]hat cannot, therefore, be determined from this investigation is the degree of skin exposure at which plasma levels of benomyl would have become detectable, which (naturally) would occur when the clearance rate of the liver was being exceeded." (TNO study at 24.)

It is the presence of the 5-HBC metabolite in the test subjects' urine samples which Drs. Howard and Tackett contend support their 3.5% dermal absorption rates for Benlate on human skin. Dr. Howard contends that the 5-HBC evidences the amount of benomyl that had at one time been absorbed through the skin of the test subjects before being excreted in their urine. (Howard 10/04/01 Dep. 53-64.) Despite the fact that no quantifiable MBC was found in the plasma of the test subjects, Dr. Howard, using the respective molecular weights of 5-HBC and the benomyl metabolite MBC, took the measured amounts of 5-HBC present in the test subject's urine to calculate what he contends is the amount of benomyl that was absorbed through their skin to become bioavailable in the form of MBC in their blood. (Howard 10/04/01 Dep. at 61.) While his specific mathematical computations of the back-calculation of 5-HBC to MBC[12] are not made a part of the record in this case, based upon this back calculation, Dr.

[12] These computations were apparently exhibits to his October 4, 2001, deposition but were not submitted to the court.

Howard contends that a 3.5% dermal absorption rate is "conservative." (*Id.* at 62-63.) Dr. Tackett adopted Dr. Howard's calculations of the amount of benomyl bioavailable in the subjects of the TNO study. (Tackett Dep. at 211, 224.)

C. *Teratogenicity*

In addition to concluding that Mrs. Bourne was exposed to benomyl which was absorbed into her body through her skin, Drs. Howard and Tackett opine that benomyl is a human teratogen, capable of causing the plaintiff's anophthalmia. They rely upon *in vivo*[13] studies, involving injections of Benlate into laboratory rats and *in vitro*[14] studies, examining the effect of Benlate on living human cells, for their assertions that benomyl is a human teratogen. The first *in vivo* study relied upon by Drs. Howard and Tackett was conducted by Dr. Robert Staples in 1980 and involved benomyl administration via stomach tube to pregnant rats at doses of 3 milligrams, 10 milligrams, 30 milligrams, 62.5 milligrams, and 125 milligrams per kilogram of body weight per day. (Ex. 9, Def.'s Mot. Exclude.) In the first of two *in vivo* studies by Dr. Staples, both sponsored by DuPont, 2 of 251 rats at the 10 milligram dose level bore offspring with microphthalmia.[15] At the 30 milligram level, 1 of 238 offspring had microphthalmia, and at the 62.5 milligram level, 10 of 213

[13] *In vivo* tests are conducted on living animals.

[14] *In vitro* tests involve the exposure of isolated cell systems to a particular substance under controlled laboratory conditions within a test tube or petri dish.

[15] Microphthalmia, a condition related to anophthalmia, involves being born with underdeveloped eyes.

offspring had microphthalmia. This study concluded that the lowest effect dose of benomyl appeared to be 10 milligrams per kilogram of weight per day. (*Id.*) In the second study, Dr. Staples found a lowest effect dose, or lowest observable effect level ("LOEL"), at 62.5 milligrams per kilogram of weight. A no observable effect level ("NOEL") of 30 milligrams per kilogram per day was adopted by Dr. Staples based upon the second study.

Drs. Howard and Tackett cite to another rat gavage study conducted by a professor at the University of California in 1991 which revealed ocular abnormalities in 43% of rat offspring at a dose level of 62.4 milligrams per kilogram of weight. E. Hoogenboom, *Effects on the Fetal Rat Eye of Maternal Benomyl Exposure,* 10 Current Eye Research 7, 601-612 (1991) (Ex. 12, Def.'s Mot. Exclude.) Another rat gavage study performed by Culick in 1981 wherein 125 milligrams per kilogram per day of benomyl were injected into pregnant rats revealed teratogenic effects. Robert Culick, *Determination of Benomyl/Methyl-2-Benzimidazole Carbamate (MBC), 4-OH MBC and 4-OH MBC Concentration in Maternal Blood and in the Concepti of Rats Exposed to Benomyl by Gavage,* Haskell Report No. 970-80. Finally, a whole body autoradiography study ("Covance study"), sponsored by DuPont, revealed a concentration of benomyl in the uveal tract, the area lining the inside of the eye behind the cornea. Whitby, C-Benomyl: *Quantitative Whole Body Autoradiography Following Oral Administration (2mg/kg) to Female Pigmented Rats,* Covance Laboratories (1998) (Ex. 49, Def.'s Mot. Exclude.)

In addition to using *in vivo* rat studies to support their contention that benomyl is a human teratogen, Drs. Howard and Tackett also used *in vitro* tests. Dr. Howard

relies upon *in vitro* tests conducted by Dr. Dick Van Velzen and Dr. Graham McLean. Dr. Tackett relied only on the *in vitro* study of Dr. McLean. Dr. Van Velzen, in studies performed in 1996 and 1997, dosed human fetal lung cells, fibroblasts, in varying concentrations of Benlate for a period of 24 hours. He then examined the cells to ascertain the smallest amount of Benlate concentration at which there was any observable effect on the cell through micronuclei[16] formation, and in 1997, through both micronuclei formation and DNA reduction. (Van Velzen Dep. at 73.) Van Velzen inferred that cell death, or aptosis, was occurring based upon the increased formation of micronuclei and a reduction in DNA. *Id.* at 74. Van Velzen found a LOEL at 25 parts per billion benomyl. (Van Velzen Dep. at 298.) He found a NOEL at 20 parts per billion benomyl. (*Id.* at 300-303.)

Dr. McLean, in a similar *in vitro* study conducted in 1997, exposed human cancer nerve cells, neuroblastomas, and rat cells, to benomyl of varying concentrations for 24 hours. (McLean Dep. at 77-78.) He reported a LOEL for the rat cells at 3 parts per billion benomyl. McLean, et al., *The Effect of Benomyl on Neurite Outgrowth in Mouse NB2A and Human SH-SY5Y Neuroblastoma Cells In Vitro,* NeuroToxicology 19(4-5):629-631 (1998).

Based upon these *in vitro* and *in vivo* tests, Drs. Howard and Tackett inferred that benomyl is a human teratogen and extrapolated the human threshold dose for teratogenicity.

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[16] Dr. Van Velzen described micronuclei as simply "very small nuclei." (Van Velzen Dep. at 73.)

D. *Epidemiology*

In reaching their opinions with respect to causation, Drs. Howard and Tackett considered three epidemiological studies relating to pesticide exposure and birth defects, but rejected those studies as irrelevant and unreliable, based upon the opinions of plaintiff's expert epidemiologist, Dr. David Ozonoff.

1. Spagnolo study

A 1994 study by A. Spagnolo was conducted "following the report of clusters of anophthalmia and microphthalmia in England and Wales and their possible relation to the pesticide Benomyl." *See* A. Spagnolo, et al., *Anophthalmia and Benomyl in Italy: A Multicenter Study Based on 940,615 Newborns,* Repro. Toxicology 8:397-403, 397 (1994). In this two-part study, the authors utilized registries of birth defects to identify 111 children with anophthalmia and microphthalmia born in Italy between 1986 and 1990, of a total of 940,615 births. After controlling for defects associated with chromosomal abnormalities, the authors divided Italy into regions and, in the first part or ecological portion of the study, examined the relationship between incidence of birth defects and use of benomyl by region. The results revealed a negative, nonsignificant coefficient, with there being a negative relationship between increased benomyl use by region and the incidence of anophthalmia and microphthalmia. *Id.* at 401.

In the second part or case control portion of the study, the authors examined the relationship between parental occupation and the incidence of children with eye defects by identifying children with anophthalmia and microphthalmia

from the birth defect registries. The authors used the birth records to identify those children with parents who worked in the agricultural field. Of the 111 children with anophthalmia and microphthalmia as just noted, information on parental occupation was available in 90 of the 111 cases. Of those 90 cases, 4 had a parent with an agricultural occupation. *Id.* at 401-02. After excluding the defects associated with chromosomal abnormalities, there were 63 cases of anophthalmia and microphthalmia in which parental occupation information was available. Two of the children had a parent with an agricultural occupation. *Id.* at 402. The second phase of the study "did not show a significant association between agricultural occupation and anophthalmia and microphthalmia at birth." *Id.* at 402.

Dr. Ozonoff contends that the Spagnolo study is "incapable of providing information on the risks of anophthalmia/microphthalmia to the offspring of exposed pregnant women from Benlate exposure." (Ozonoff report at 5.) He maintains that the study does not examine the relationship between prevalence of exposure and prevalence of a health outcome inasmuch as the study does not measure individual exposure to benomyl, but instead compares disease prevalence with benomyl's use by region in Italy. (*Id.* at 68.) He contends that the results are "fundamentally uninterpretable in terms of the risks of Benlate to individuals."[17] (*Id.* at 9.) In his report, Dr. Ozonoff does not mention the second portion of the study

[17] Dr. Alexander M Walker, M.D., Ph.D., DuPont's expert epidemiologist, testified that he does "not rely on the ecological portion of the Italian study for [his] opinion." (Walker Aff. at ¶ 26.)

examining parental occupation and its relationship to anophthalmia and microphthalmia except to state in a conclusory manner that an exposure surrogate,[18] consisting in this instance of parental occupation as an agricultural worker, for benomyl exposure is likely to be misclassified. (*Id.* at 12.)

In his evidentiary deposition, Dr. Ozonoff expounded on his report by stating that one who was employed as an agricultural worker in Italy during the relevant time period was not necessarily exposed to benomyl. (Ozonoff Dep. Dec. 17, 2001, Depo. at 154-56.) He testified that even assuming farm workers were exposed to benomyl, the subjects could have been all male or non-pregnant females, which would not have yielded useful results. (*Id.*) He also indicated that, while birth defect registries are mandatory, it is quite common that they aren't filled in, making it difficult to tell whether all the cases of a particular defect were properly recorded. (*Id.* at 150-51.) Upon cross-examination, Dr. Ozonoff testified that while not desirable, the use of exposure surrogates is common in epidemology. (*Id.* at 96-97.)

Dr. Ozonoff also testified that it would be "possible" but "extremely difficult" to design and conduct an epidemiology study to test the hypothesis of whether or not

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[18] Explaining the term "exposure surrogate," Dr. Ozonoff testified, "[s]ometimes you just don't have that information, especially if it's something that occurred in the past when nobody was around to observe it or if it's too expensive to obtain that information by interviewing everybody, so you try and use some indicator of what exposure might have been; for example, an occupation, and some occupations will be much better exposure surrogates than others for particular exposures." (Ozonoff Dep. Dec. 17, 2002, at 98.)

there is an association between benomyl exposure and anophthalmia. While he testified that he doesn't "know very much about . . . the prevalence of Benlate exposure" in different populations, he stated that where the outcome, anophthalmia, is rare, and the exposure to benomyl is rare as well, "there is no real design you can use." (Ozonoff Dep. Dec. 17, 2001, at 129.) He refers to no studies or reports to support his opinion about the difficulty of designing such a study. Nor does he set parameters for what level of exposure and/or outcome would constitute "rare." He testified that if exposure to Benlate is not rare, then it would be possible to design a case control study examining the association between benomyl exposure and anophthalmia. (*Id.* at 130.)

2. Kristenson study

In a study published in 1997, the authors examined the relationship between the prevalence of birth defects as reported to the Medical Birth Registry of Norway from 1969 to 1989 out of a total of 192,417 births, and parental occupations in farming. The study found significant correlations between parental occupation in farming and several birth defects, but not eye malformations. P. Kristenson, et al., *Birth Defects Among Offspring of Norwegian Farmers,* Epidemiology 8:537-44 (1997). This 1997 published study does not mention benomyl but refers only to pesticides generally. However, in a letter to the editor of the British Medical Journal published in 1994, Kristenson offered an additional description of the same study and its results. The letter states in relevant part:

> Benomyl was introduced in Norway in 1971. It is mainly used as a fungicide in greenhouses and orchards; it is also used to a limited extent during the spring in fields of vegetables and, since

> the mid-70s, in the late autumn in the grain fields. Its use has been limited in Norway: the maximum sale was 1682 kg active compound in 1980. We considered farm activities after 1970 that might result in exposure of benomyl at a relevant time: work in greenhouses throughout the year; in orchards for children conceived in April-June; with vegetables grown in fields for children conceived in August-November. Eleven percent (n=21843) of the entire cohort of infants born in 1967-91 had potentially been exposed to benomyl according to these criteria. Four of the 192416 [sic] children had been diagnosed as having anophthalmia or microphthalmia. . . . Our data do not indicate that parental agricultural activity is a specific risk for anophthalmia in children. Even with this large cohort, comprising roughly a seventh of all births in Norway during the period studied, no firm conclusions concerning this rare birth defect can be drawn. The use of proxies as exposure variables adds to the uncertainty. Nevertheless, our data do not support the suggestion that benomyl is a risk factor.

Kristenson, P. "*Clusters of anophthalmia: No link with benomyl in Italy . . . or in Norway.*" BMJ, 308: 206-207, 1994.

Dr. Ozonoff disregards the Kristenson study because the 1997 published study does not mention benomyl but refers only to pesticides generally. With respect to the letter to the editor by Kristenson which appears to further describe the results of his study as it related to benomyl, Dr. Ozonoff maintained simply that the study "is not informative as to the question of whether [bemomyl is] a risk factor." (Ozonoff Dep. Dec. 17, 2001, at 85.) In his report he also noted that the study might have erroneous

results as a consequence of the failure to recognize less conspicuous forms of microphthalmia or cases in which microphthalmia is a concomitant malformation, and because the use of Benlate in Norway was very restricted during the relevant time. (Ozonoff Rep. at 11.) Neither his report nor his evidentiary deposition explain the basis for his statement that the use of Benlate in Norway was then very restricted.

3. Dolk study

A study examining geographical variation in anophthalmia and microphthalmia in England published in 1998 investigated the allegations of an English newspaper that there were "clusters" of blind children in England in farming areas associated with Benlate use. H. Dolk, et al., *Geographical Variation in Anophthalmia and Microphthalmia in England, 1988-1994,* British Medical Journal, 317:905-09. The study found that the overall prevalence of anophthalmia and microphthalmia in England was 1 in 10,000 births and found no statistically significant variation from region to region of England. *Id.* at 907.

Dr. Ozonoff does not discuss the Dolk study in his report except to state that "the existing data from England and Norway is similarly without relevance to this question [the risk of anophthalmia and microphthalmia to the offspring of exposed pregnant women to Benlate]."[19]

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[19] Dr. Ozonoff testified at his discovery deposition taken October 23, 1998, that at the time he drafted his report, he had not read the Dolk study, which had not yet been published. (Ozonoff Dep. October

(Continued on following page)

Dr. Howard and Dr. Tackett both relied upon Dr. Ozonoff's opinions regarding the irrelevance of the epidemiological studies relating to Benlate use and anophthalmia and microphthalmia. (Howard report at 1.) Inasmuch, however, as Dr. Ozonoff acknowledged that the use of exposure surrogates, as in the Spagnolo study, is common in the field of epidemiology, and considering he provided only conclusory and speculative remarks about the Kristenson study and the Dolk study, it appears that the blanket rejection by Drs. Howard and Tackett of these epidemiological studies was unfounded. The court finds this particularly to be true when plaintiff had pointed to no epidemiological evidence supportive of his position.

III.

DuPont seeks to exclude the testimony of Drs. Howard and Tackett on several grounds. DuPont asserts that (1) Drs. Howard and Tackett are not qualified to render the opinions they offer; (2) they failed to perform a differential diagnosis of the plaintiff; (3) the methodologies of Drs. Howard and Tackett of relying upon single-species high dose animal studies and *in vitro* cell culture tests, without relying upon relevant epidemiological data, to draw conclusions about human teratogenesis via dermal absorption, is not scientifically valid, reliable, or generally accepted pursuant to Federal Rules of Evidence 104, 402, and 702; (4) Dr. Howard's calculations of the dose of Benlate to which Mrs. Bourne was exposed, and Dr.

23, 1998, at 19.) He testified that reading the study did not alter his opinion. (*Id.* at 19-20)

Tackett's ratifications thereof, are imprecise and invalid; (5) the dermal absorption rates utilized by Drs. Howard and Tackett were derived using unreliable and scientifically invalid bases; and (6) Drs. Howard and Tackett misuse EPA and EU regulatory processes and recommendations as if they were causation determinations.

In response, plaintiff asserts that, while each piece of data underlying the conclusions of Drs. Howard and Tackett may not be sufficient to independently justify the experts' conclusions, taken as a whole the body of data relied upon by Drs. Howard and Tackett support their conclusions, rendering their methodologies sound.

IV.

Effective December 1, 2000, Federal Rule of Evidence 702 was amended to reflect the United States Supreme Court's landmark decision of *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). The revised Rule 702 states:

> Testimony by Experts – If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed.R.Evid. 702. As the Advisory Committee Notes indicate, the amendment to Rule 702 is consistent with the

district court's "gatekeeping" function as articulated in *Daubert*. The proponent of the proposed expert testimony must establish its admissibility by a preponderance of proof. *See Daubert*, 509 U.S. at 592 n. 10, 113 S.Ct. 2786; Fed.R.Evid. 104(a).

In *Daubert*, the United States Supreme Court charged trial judges with the responsibility to act as "gatekeepers" to "ensure that any and all scientific testimony . . . is not only relevant, but reliable." *Daubert*, 509 U.S. at 589, 113 S.Ct. 2786. As a part of its analysis, a trial court is to determine "whether the expert is proposing to testify to (1) scientific knowledge that (2) will assist the trier of fact to understand or determine a fact in issue." *Id.* at 592, 113 S.Ct. 2786. It is for the trial court to make the "preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." *Id.* at 592-93, 113 S.Ct. 2786. As to the first prong of the inquiry, whether the expert offers "scientific knowledge," the analysis focuses on whether the subject of the expert's testimony is grounded in the "methods and procedures of science," and constitutes "more than subjective belief or unsupported speculation." *Id.* at 590, 113 S.Ct. 2786. In order to qualify as "scientific knowledge," an inference or assertion must be derived by the "scientific method." *Id.* That is, the testimony must be supported by "'good grounds,' based on what is known." *Id.*

The Supreme Court in *Daubert* set forth a flexible, non-exhaustive checklist of four factors for trial courts to utilize in their evaluations of reliability. *Id.* at 593-94, 113 S.Ct. 2786. These factors include: (1) whether a theory or technique can be or has been tested; (2) whether it has

been subjected to peer review and publication; (3) whether a technique has a high known or potential rate of error and whether there are standards controlling its operation; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community. *Id.* at 592-94, 113 S.Ct. 2786. In a later opinion, the Court further emphasized that these factors are flexible, not rigid, may or may not be pertinent in a given case and are to be applied based upon "the particular circumstances of the particular case at issue." *Kumho Tire Co. v. Carmichael,* 526 U.S. 137, 150, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999).

The second prong of the *Daubert* analysis focuses on whether the expert's testimony will be helpful to the trier of fact in deciding a fact in issue. Included in that analysis is the question of relevancy or "fit." *Id.* at 591, 113 S.Ct. 2786. The expert's proffered scientific testimony must be sufficiently tied to the facts of the case that it will be of assistance to the factfinder in resolving a disputed fact. *Id.* (citing *United States v. Downing,* 753 F.2d 1224, 1242 (3rd Cir.1985)). That is, there must be a "valid scientific connection to the pertinent inquiry" before the testimony is admissible. *Id.* at 591-92, 113 S.Ct. 2786.

The Court noted in *Daubert* that "vigorous cross examination, presentation of contrary evidence and careful instruction on the burden of proof are traditional and appropriate means of attacking shaky but admissible evidence." *Daubert,* 509 U.S. at 596, 113 S.Ct. 2786. However, when making the determination as to admissibility, a trial judge has considerable leeway in both the determination of reliability and the means the judge uses to make it. *See Kumho Tire Co.,* 526 U.S. at 152, 119 S.Ct. 1167.

V.

The court does not propose to question the qualifications of Drs. Howard and Tackett for purposes of this order.[20] The court must determine, pursuant to *Daubert,* first, whether the proffered testimony constitutes "scientific knowledge," grounded in the "methods and procedures of science," and is "more than subjective belief or unsupported speculation," and second, whether the proffered testimony "fits" with the factual inquiry of the case. *See Daubert,* 509 U.S. at 589-91, 113 S.Ct. 2786.

A. *General Causation*

Drs. Howard and Tackett have derived their general causation theory, that benomyl is teratogenic to humans, based solely upon *in vivo* rat gavage studies and *in vitro* tests. They discredit the only existing human data, consisting of epidemiological studies reflecting no statistical relationship between potential Benlate exposure and human birth defects. They also disavow gavage benomyl testing on different animal species – the mouse and the rabbit – which have revealed no ocular abnormalities in the offspring.

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[20] In a rather factually similar civil action, *E.I. DuPont De Nemours & Co., Inc. v. Castillo,* 748 So.2d 1108 (Fla. 3d DCA), *review granted,* (Fla.2000) ("*Castillo*"), wherein plaintiff alleged that his mother's dermal exposure to Benlate caused his anophthalmia, the intermediate appellate court of Florida excluded the testimony of Dr. Howard but found nonetheless that he was qualified under the Florida Rules of Evidence to render his proffered opinions. The Florida Supreme Court granted certiorari and oral arguments were presented on February 6, 2001.

There can be no dispute that properly designed and conducted animal testing can yield relevant and useful information in the field of human toxicology. *See, e.g., Turpin v. Merrell Dow Pharmaceuticals, Inc.*, 959 F.2d 1349, 1360-61 (6th Cir.1992), *cert. denied*, 506 U.S. 826, 113 S.Ct. 84, 121 L.Ed.2d 47 (1992) ("We do not mean to intimate that animal studies lack scientific merit or power when it comes to predicting outcomes in humans. Animal studies often comprise the backbone of evidence indicating biological hazards, and their legal value has been recognized by federal courts and agencies. Here, the record's explanation of the animal studies is simply inadequate. . . . The record fails to make clear why the varying doses of Bendectin or doxyalamine succinate given to the rats, rabbits and *in vitro* animal cells would permit a jury to conclude that Bendectin more probably than not causes limb defects in children born to mothers who ingested the drug at prescribed doses during pregnancy."). Likewise, *in vitro* tests provide useful information about metabolic processes at a cellular level, and may supplement existing animal and human data. *See, e.g., Allen v. Pennsylvania Engineering*, 102 F.3d 194, 198 (5th Cir.1996) (*in vitro* data shows only that ethylene oxide has mutagenic and genotoxic capabilities in living organisms, not that it necessarily causes brain cancer in humans). However, the extrapolations of Drs. Howard and Tackett, from high-dosage, single species *in vivo* testing and lengthy benomyl exposure *in vitro* testing, to conclude that benomyl is a human teratogen and to establish the levels at which it is alleged to be teratogenic, are neither reliable, pursuant to the first prong of *Daubert*, nor relevant, under the second prong.

Courts considering the reliability of experts' extrapolation to human teratogenicity from *in vivo* and *in vitro* tests have recognized that such tests are generally considered to be suspect when relied upon for that purpose. In the absence of other strong indicators of the reliability of *in vivo* and *in vitro* tests, including supporting epidemiological studies, testing on closely related species,[21] and the use of comparable dosages, courts have overwhelmingly found unreliable the methodology of extrapolating human teratogenicity from *in vivo* and *in vitro* tests. *See, e.g., Raynor v. Merrell Pharms., Inc.,* 104 F.3d 1371, 1374 (D.C.Cir.1997) (concluding it was not methodologically sound for experts to draw inference from chemical structure studies, *in vivo* animal studies, and *in vitro* studies, that Bendectin caused human birth defects, when epidemiological evidence was to the contrary); *Allen,* 102 F.3d at 198 (excluding expert testimony as unreliable where *in vivo* tests were inconclusive and *in vitro* tests could not be extrapolated to establish human teratogenicity); *Conde v. Velsicol Chem. Corp.,* 24 F.3d 809, 813 (6th Cir.1994) (finding experts were unable to connect chemical chlordane with plaintiffs' injuries using *in vivo* and *in vitro* tests, in light of plaintiffs' low level of exposure to the substance and contradictory epidemiological evidence); *Sorensen v. Shaklee Corp.,* 31 F.3d 638, 646 n. 12 (8th

[21] Primates are considered to render the most persuasive results with respect to extrapolation of the results to humans, followed by other mammals, then birds, followed by reptiles. *See* Erica Beecher-Monas, *The Heuristics of Intellectual Due Process: A Primer for Triers of Science,* 75 N.Y.U.L.Rev. 1563, 1608 (2000) (citing Larry C. Gilstrap & Bertis B. Little eds, *Drugs and Pregnancy* 9 (2d ed.1998) (noting that "nonhuman primates are better predictors . . . than are nonprimate models because they are phylogenetically close to humans")).

Cir.1994) ("Because of the dose-response differential between animals and humans, however, extrapolating to humans from animal studies is problematic."); *Turpin,* 959 F.2d at 1360-61 ("The record fails to make clear why the varying doses of Bendectin or doxyalamine succinate given to the rats, rabbits and *in vitro* animal cells would permit a jury to conclude that Bendectin more probably than not causes limb defects in children born to mothers who ingested the drug at prescribed doses during pregnancy.");[22] *Richardson v. Richardson-Merrell, Inc.,* 857 F.2d 823, 830 (D.C.Cir.1988), *cert. denied,* 493 U.S. 882, 110 S.Ct. 218, 107 L.Ed.2d 171 (1989) (finding that chemical structure activity analysis and *in vitro* and *in vivo* studies used by plaintiff's expert cannot furnish sufficient foundation for causation opinion in the face of considerable contrary epidemiological evidence); *Lynch v. Merrell-Nat'l*

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[22] The court in *Turpin,* referring to an authoritative text on teratology, explained why animal testing cannot be directly extrapolated to human beings:

> "A recognized text on teratology states the customary scientific view that 'it has become axiomatic in experimental teratology that agents capable of causing any adverse biological effects can usually also be shown to be embryotoxic under the right conditions of dosage, developmental stage, and species susceptibility,' and that 'virtually all drugs and a great range of chemicals can indeed be shown to be embryotoxic under appropriate laboratory conditions. . . .' The author concludes that to 'eliminate drugs and chemicals because they can be shown to be embryotoxic at high dosage would be unacceptable' because to do so 'would eliminate most drugs and many useful chemicals upon which modern society depends heavily.'"

Turpin, 959 F.2d at 1359 (quoting James Wilson, Current Status of Teratology, in *Handbook of Teratology* 60 (J. Wilson & C. Fraser, eds.1977)).

Labs., 830 F.2d 1190, 1194 (1st Cir.1987) (*in vivo* and *in vitro* animal tests and the tests on "analogous" chemicals, whether "singly or in combination, do not have the capability of proving causation in human beings in the absence of any confirmatory epidemiological data"); *Wade-Greaux v. Whitehall Laboratories, Inc.,* 874 F.Supp. 1441, 1484 (D.Vi.1994), *aff'd.,* 46 F.3d 1120 (3rd Cir.1994) (excluding causation experts' opinion, finding high dose animal testing and *in vitro* animal test data are not relied upon by experts in the field of teratology for extrapolating the results found directly to the human experience); *In re Agent Orange Product Liab. Litig.,* 611 F.Supp. 1223, 1241 (E.D.N.Y.1985), *aff'd,* 818 F.2d 187 (2d Cir.1987), *cert denied,* 487 U.S. 1234, 108 S.Ct. 2898, 101 L.Ed.2d 932 (1988) ("[L]aboratory animal studies . . . are generally viewed with more suspicion than epidemiological studies, because they require making the assumption that chemicals behave similarly in different species.").

The only existing epidemiological evidence[23] is contrary to plaintiff's position. Further, *in vivo* benomyl testing has revealed ocular abnormalities in only a single species of animal, whereas gavage testing on both the

[23] Drs. Howard and Tackett rely upon the opinion of Dr. Ozonoff, a physician and environmental epidemiologist, discrediting the validity of the epidemiological evidence relating to benomyl. Even assuming this methodology – reliance upon the opinion of an expert in the field of epidemiology – is sound, the plaintiff has no epidemiological evidence supporting the proposition that benomyl is a human teratogen. He is left, therefore, with only rat gavage tests and *in vitro* tests to extrapolate both human teratogenicity of benomyl and the levels of the substance capable of causing birth defects. *See supra* II.D.

rabbit and the mouse revealed no ocular abnormalities.[24] The court concludes that Drs. Howard and Tackett have failed to offer sufficient support for the otherwise suspect single-species *in vivo* tests and *in vitro* tests to render methodologically sound an extrapolation of human teratogenicity.

Moreover, the rat gavage studies and the *in vitro* tests relied upon by Drs. Howard and Tackett, using injections of high-levels of benomyl directly into the stomach of rats and high-level *in vitro* dosing of cells of both rats and humans in benomyl for 24 hours, do not "fit" with the facts of the case as alleged. *General Elec. Co. v. Joiner,* 522 U.S. 136, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997), is germane. In *Joiner,* a city electrician who suffered from lung cancer filed suit against the manufacturer of polychlorinated biphenyls (PCBs) and manufacturers of electrical transformers and dielectric fluid, alleging strict liability, negligence, fraud, and battery. The district court excluded the testimony of electrician experts and granted defendants'

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[24] *See* R. Kavlock, et al., *Teratogenic Effects of Benomyl in the Wistar Rat and CD-1 Mouse, with Emphasis on the Route of Administration,* Toxicol. Appl. Pharmacol., 62: 44-54 (1982) (Ex. 11, Def.'s Mot. Exclude); W. Busey, Segment II – *Teratology Study in Rabbits,* Hazleton Leboratoris, Inc. (Unpublished Report No. MRO 1079) (1968) (Ex. 13, Def.'s Mot. Exclude); S. Munley, *Developmental Toxicology Study of DPX-T1991-529 (Benomyl) in Rabbits,* Newark, Delaware, E.I. DuPont de Nemours and Co., Inc., Haskall Laboratory (Unpublished Report No. HLR 164-95) (1995) (Ex. 14, Def.'s Mot. Exclude).

Dr. Tackett acknowledged at deposition that one species of animals will generally have a different teratogenic response to a chemical than will another animal species. (Tackett Dep. at 224.) Dr. Howard testified, "[i]t's usually said that to define something as a human teratogen it's desirable to have two animal models." (Howard Dep. at 672.)

motion for summary judgment. The United States Court of Appeals for the Eleventh Circuit reversed. The Supreme Court considered the fact that the plaintiff's proffered causation expert relied upon studies indicating that infant mice developed cancer of a different type than the plaintiff, after receiving massive gavage doses of PCBs. *Id.* at 144, 118 S.Ct. 512. The Court noted that the experts never explained "how and why [they] could have extrapolated their opinions from animal studies "far removed" from the circumstances of the plaintiff's exposure to PCBs." *Id.* Finding the studies upon which the experts relied to be "not sufficient, whether individually or in combination, to support their conclusions," the Court found that the district court had not abused its discretion in excluding their testimony. *Id.* at 146, 118 S.Ct. 512.

Similarly, the rat gavage testing relied upon by Drs. Howard and Tackett is "far removed" from the plaintiff's alleged exposure, with high doses of benomyl injected directly into the rats' stomachs. Using the Staples studies as an example, the lowest level of benomyl injection at which an ocular effect on offspring was noted was at 10 milligrams per kilogram of weight per day. A comparable dosage for Mrs. Bourne, who weighs approximately 50 kilograms, would be a direct injection (setting aside the fact that the chemical is alleged to have been absorbed dermally at a rate of 3.5%) of 500 milligrams, or one-half of one gram. Each sachet of Benlate contained approximately 1.19 grams of benomyl (based on 53% of the 2 .25 gram Benlate sachet). Thus, to be comparable to the lowest observable effect level, approximately one-half of the contents of a sachet would have to be injected into Mrs. Bourne. The other rat studies relied upon by Drs. Howard and Tackett involved far greater injections of

benomyl.[25] Indeed, none of the rat studies producing teratogenic effects involved exposure to benomyl dermally or orally. With respect to the *in vitro* tests wherein cells were continually soaked in benomyl for 24 hours, plaintiff has made no contention that Mrs. Bourne was continually and directly exposed to benomyl for such an extended period. In sum, the analytical gap between the rat evidence relied upon by Drs. Howard and Tackett and the inferences drawn therefrom is simply too wide, rendering the extrapolations a poor "fit" for the facts of the case.

The court concludes that the methodologies of Drs. Howard and Tackett in concluding that benomyl is a human teratogen are unsound.

B. *Specific causation*

Even assuming, *arguendo,* that the extrapolations from *in vivo* rat studies and *in vitro* studies to human teratogenicity levels were scientifically sound, the court nonetheless concludes that the opinions of Drs. Howard and Tackett relating to specific causation are not scientifically valid and reliable.

It appears that the conclusion of Dr. Howard, as adopted by Dr. Tackett, with respect to Mrs. Bourne's level of dermal exposure to Benlate, is highly speculative, without the indicia of reliability required by Rule 702 and *Daubert.* Rather than conducting any type of test or study

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[25] Staples second rat study produced a LOEL at 62.5 milligrams per kilogram; the Culick study injected 125 milligrams per kilogram; the Hoogenboom study used 62.4 millograms per kilogram of weight. *See supra* p. 15-17.

to attempt to recreate the actions described by Mrs. Bourne in her deposition with respect to treating her plants with Benlate, it appears that Dr. Howard has developed arbitrary figures to represent what he deems to be the percentage of Mrs. Bourne's body exposed to Benlate and the amount of the Benlate mixture applied to her skin which he calculates to be 5% of the one-gallon Benlate mixture used periodically by her. While he contends on the one hand that the figure is based upon the portion of a gallon estimated by him as necessary to produce the level of wetness described by Mrs. Bourne, he also testified that he back-calculated the amount of dermal benomyl exposure necessary, using a 3.5% dermal absorption rate, to achieve a benomyl concentration of 20 parts per billion. (Howard Dep. at 117.) Thus, Dr. Howard's 5% figure is, at best, purely speculative and at worst, devised to ensure that a certain desired end – 20 parts per billion – was met. In either case, the adopted methodology, or lack thereof, is contrary to principles of sound scientific method. *See, e.g., General Elec. Co. v. Joiner,* 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997) ("nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* [an assertion made but not proved] of the expert"); *Oglesby v. General Motors Corp.,* 190 F.3d 244, 250 (4th Cir.1999) ("A reliable expert opinion must be based on scientific, technical, or other specialized knowledge and not on belief or speculation, and inferences must be derived using scientific or other valid methods.").

Additionally, the 5% figure does not take into account pertinent published studies (DuPont Everhart study and NIOSH Hoekstra study, *supra* p. 8-9) examining the

exposure of garden users to Benlate. *See, e.g., Cooper v. Smith & Nephew, Inc.,* 259 F.3d 194, 203-04 (4th Cir.2001) (affirming trial court's exclusion of plaintiff's causation expert, in part, on basis that expert rejected, without offering sound explanation, medical literature and plaintiff's own medical records which tended to support another cause of plaintiff's condition). Nor is the 5% calculation capable of being tested or reproduced. *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579, 592-94, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993) (setting forth non-exhaustive list of factors pertinent to whether an opinion is reliable); *United States v. Dorsey,* 45 F.3d 809, 814-815 (4th Cir.1995) (affirming exclusion of expert testimony as scientifically invalid because the methodology upon which it was based was not generally accepted, had never been peer-reviewed, and its potential rate of error was high). In sum, Dr. Howard's methodology in arriving at the 5% figure, is unreliable.

The methodology utilized by Drs. Howard and Tackett in deriving a level of human dermal absorption for benomyl likewise appears to be unsound. In his report, Dr. Howard utilized several dermal absorption rates, the lowest thereof being 2%. He identifies several sources for the dermal absorption rates, including the EPA's use of a 3.5% rate and the amount of Benlate "potentially absorbed" by the test subjects in the TNO studies. The EPA's use of a 3.5% figure is based upon a 1979 study on the dermal absorption of Benlate on rat skin wherein 3.5% was absorbed after a period of 10 hours. *See supra* p. 9. Setting aside the fact that it is not alleged that Mrs. Bourne was exposed to Benlate for a 10 hour period, it is well established among the scientific community that rat skin is more permeable than human skin. (*See* Maibach

Aff. at ¶ 48; Tackett Dep. at 126-27.) Dr. Tackett testified in his deposition that he believes that rabbit skin and rat skin are approximately 10 times more permeable than human skin with respect to Benlate or benomyl. While his report does not identify a specific rate which he has adopted, it mentions the EPA's 3.5% dermal absorption rate, based on rat studies, and formulated for risk assessment, not causation, purposes. (Tackett Report at 4.) The only study relied upon by Drs. Howard and Tackett relating to the dermal absorption of benomyl on living human skin is the TNO study conducted by Mueling.[26] (*See* Mueling, TNO Lab Reports V3596 and V2662.) Mueling testified at deposition that based on the TNO study he was not able to determine a rate of benomyl transmission through the human skin, nor was he able to ascertain whether the rate of percutaneous absorption of benomyl is dependent upon the amount of skin which is exposed. (Mueling Dep. at 77.) The TNO study found no measurable amounts of benomyl metabolites in the blood plasma of the test subjects. (*See* W. Mueling, TNO Lab Reports *supra* 38.)

Despite the seeming lack of useful results produced by the TNO study,[27] Drs. Howard and Tackett rely upon the

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[26] A study conducted on human cadavers revealed a dermal absorption rate for benomyl of less than 1%. (ICI Central Toxicology Laboratory, Report CTL/P/3659.)

[27] Mueling testified that the TNO study failed to determine the following: the rate of transmission of benomyl through human skin; the levels achieved of the major metabolites of benomyl in blood plasma; the time it takes for benomyl metabolites to reach a peak concentration in blood plasma or how long that peak concentration persists; the speed or time at which the level of benomyl metabolites begin to drop off; the half-life of benomyl metabolites in blood plasma; whether the rate of percutaneous absorption of benomyl is dependent on or changes with

(Continued on following page)

detectable amounts of 5-HBC in the test subjects' urine to calculate what they contend to be the dermal bioavailability of benomyl. They back-calculate the cumulative amount of benomyl and its metabolite MBC that passed through the blood and tissue of the human test subjects in the TNO study by converting the total amount of 5-HBC found in the urine of the test subjects, assuming benomyl is approximately 138% of the molecular weight of 5-HBC. (Howard Dep. at 83-85.) As DuPont's expert pharmacologist and toxicologist Michael Owens, PhD, points out, this methodology is based on the "unsupported assumption that all of the 5-HBC in the urine was at one point benomyl/MBC in the blood plasma or tissue." (Owens Aff. at ¶ 7a.) It ignores the possibility that benomyl/MBC was metabolically converted to 5-HBC in the skin, prior to reaching the blood. (*Id.*) The skin's conversion of benomyl to 5-HBC, is, according to Dr. Owens, the "most likely" scenario, supported by the lack of any measurable amount of benomyl or MBC found in the blood of the TNO test subjects. (*Id.*) Further, the back-calculation fails to account for the amounts of 5-HBC which were detected in the urine, or for that matter the MBC detected in the plasma, of the test subjects prior to administration of Benlate. *See supra* II.B.

It appears that the back-calculation of 5-HBC to benomyl is internally inconsistent with the very TNO study upon which Drs. Howard and Tackett purport to

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the amount of skin exposed; whether the rate of percutaneous absorption of benomyl was dependent on or changed with the amount of substance (dose) applied to a given area; and any kinetic parameters for benomyl in humans. (*See* Mueling Dep. at 76-78.)

rely. The conductor of the study, Mueling, testified at deposition that one cannot ascertain the amount of MBC or 5-HBC in the blood based on the TNO urine data. (Mueling Dep. at 107-08.) Mueling also testified that his TNO study did not reveal a rate of transmission through human skin. (*Id.* at 76-78.) The court concludes that the calculations of Dr. Howard, adopted by Dr. Tackett, purporting to reflect the rate of human dermal absorption of benomyl into the blood based upon the amount of 5-HBC found in the urine of the TNO test subjects constitutes merely the "*ipse dixit*" of Drs. Howard and Tackett and is not grounded in "the methods or procedure of science." *See General Elec. v. Joiner,* 522 U.S. at 146, 118 S.Ct. 512.

Whether derived from the molecular weight of irrelevant 5-HBC metabolites in TNO test subjects' urine or extrapolated directly from the 20-year old Belasco tests involving the administration of benomyl to permeable rat skin for extended durations, the 3.5% dermal absorption rate used by Drs. Howard and Tackett cannot be said to be methodologically sound.

VI.

It appearing that the opinions proffered by Drs. Howard and Tackett meet neither the requisite standards of reliability or relevance under Federal Rule of Evidence 702, as set forth by the United States Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993) and its progeny, the court concludes that their testimony must be excluded.

Wherefore, for the foregoing reasons, it is ORDERED that DuPont's motion to exclude the testimony of Dr. Howard and Dr. Tackett be, and it hereby is, granted.

The Clerk is directed to forward copies of this order to all counsel of record and to post this published opinion at *http://www.wvds.uscourts.gov.*

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

ANDREW BOURNE , a minor by and through his Parents, next friends and natural guardians, Chris Bourne and Maggie Bourne,

Plaintiff

v. Civil Action No. 2:97-0090

E.I. DUPONT DE NEMOURS AND COMPANY, INC.,

Defendant

MEMORANDUM ORDER*

This matter is before the court on the motion of defendant E.I. DuPont De Nemours and Company, Inc. ("DuPont") to, exclude the testimony of Dr. Charles Vyvyan Howard and Dr. Randall L. Tackett, plaintiff's causation experts in the above-styled toxic tort action, filed December 5, 2001. Inasmuch as plaintiff's principal expert, Dr. Howard, has been extensively deposed on multiple occasions and Dr. Tackett has also been deposed and inasmuch further as the motion has been the subject of extensive submissions by both parties, the court concludes and the parties agree that the record is complete and a hearing on the motion is not needed.

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* Any typographicals found in the following Memorandum Order were left intentionally to show how the original document appeared.

I.

Minor plaintiff Andrew Bourne ("Bourne") by and through his parents, Christopher Bourne ("Mr. Bourne") and Maggie Bourne ("Mrs. Bourne"), all residents of Essex, England, filed this action in February of 1997 against DuPont alleging that Mrs. Bourne's exposure to the DuPont-manufactured agricultural fungicide Benlate, while pregnant with the plaintiff, caused plaintiff to be born with severe birth defects.[1]

Mrs. Bourne contends that she purchased Benlate from a local nursery to use in her home garden in March of 1986. (Mrs. Bourne Dep. at 39-41.) The Benlate was packaged in small sachets roughly the size of an individual-serving sugar packet, with each sachet containing 2.25 grams of Benlate powder, approximately 53% of which was comprised of Benlate's active ingredient, the chemical benomyl. (Upstone Aff. at 5.) Also supplied with the Benlate were separate sachets containing 3.0 grams of a surfactant called "Activex." (*Id.*) According to the directions contained in the package of Benlate, each sachet of Benlate powder was to be mixed with a sachet of Activex along with one UK gallon of water, approximately 4.5 liters, before application on plants. (*See* copy of Benlate label, attached as Ex. C to Upstone Aff.)

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[1] During the pendency of this case, as will be more fully noted, the parties have engaged in studies of Benlate's active ingredient, benomyl, and any relationship it may have to plaintiff's anophthalmia (the complete absence of eyes). The defendant completed and made available a pharmacokinetic study in early 1999. To rebut that study, the plaintiff was then allowed the time required to undertake a human dermal absorption study ("TNO study") that was completed in June, 2000. Plaintiff was permitted still further time to pursue a follow-up to that study that was completed in March, 2001.

Mrs. Bourne contends that she followed the instructions and mixed a sachet of the Benlate and a sachet of the Activex in a gallon of water. Mrs. Bourne says that she sprayed the entire gallon of the Benlate-Activex-water mixture (hereinafter "Benlate mixture") on her home garden every ten to twelve days from March through late June, 1986. (Mrs. Bourne Dep. 39, 45-47, 68.) She testified at deposition that she applied the Benlate mixture liberally to her beans, strawberries, and roses, using a watering can, and when the beans grew taller, using both a watering can and a hand sprayer. (*Id.* at 38-40, 43-46, 91.) She testified that it took her approximately 45 minutes to one hour to mix and apply the Benlate mixture to her plants. (*Id.* at 105.)

Mrs. Bourne wore no gloves or protective face covering while working with the Benlate. (*Id.* at 98-100.) She testified that some Benlate powder got on her hands when she prepared the Benlate mixture and that the Benlate mixture got on her hands and Benlate mixture and that the Benlate mixture got on her hands and perhaps her legs as she mixed. (*Id.* at 84-85.) When applying the Benlate mixture to her plants, she testified that the solution would get on her hands, legs, feet, and possibly face. (*Id.* at 85, 92-94, 96-97, 109.) She would bathe every day or every other day. (*Id.* at 128.)

Mrs. Bourne became pregnant with the plaintiff on or about May 5, 1986. (Ravits Dep. at 5-6.) The child was born on January 27, 1987, with bilateral clinical anophthalmia (the complete absence of eyes), hypogonadatropic hypogonadism (a pituitary disorder resulting in this case in small stature and underdeveloped genitalia), and mental retardation. (Mrs. Bourne Dep. at 128.) It is plaintiff's contention that his mother's repeated exposure

to Benlate during critical periods in his fetal development led to his birth defects. (Pl.'s Compl. at ¶ 39.)

II.

In a toxic tort case, a plaintiff must generally establish both general and specific causation for his injuries. Bourne must establish that he, via his pregnant mother, was exposed to a human teratogen, both at a level and by a means capable of causing his birth defects. He must also establish that the exposure to the teratogen did, in fact, bring about his particular maladies. Drs. Howard and Tackett both opine that Mrs. Bourne was exposed to Benlate, which they contend to be a human teratogen, at a critical stage in her son's fetal development, with the Benlate being absorbed into her blood stream at a level capable of causing Bourne's defects. They rule out genetic causes for Bourne's birth defects, and each opines that Mrs. Bourne's Benlate exposure is more likely than not the cause of her son's anophthalmia. In their reports, neither Dr. Howard nor Dr. Tackett refers to the cause of the plaintiff's birth defects other than the anophthalmia.

Dr. Howard is the senior lecturer at the University of Liverpool in the Faculty of Medicine. He is a licensed medical practitioner and a fetal toxio-pathologist. According to his report, in reaching his conclusions, Dr. Howard relied upon various studies and reports involving Benlate, the deposition transcripts of the Bournes, reports of plaintiff's expert witnesses and plaintiff's physicians, the existing epidemiology studies[2] on Benlate, the United

[2] Epidemiological studies examine the pattern of disease in human populations.

States Environmental Protection Agency ("EPA") and the European Community's classification of benomyl, his personal knowledge and experience, and "information previously identified in [his] deposition in this case and those taken in *Castillo*." (*Id.* at 1.)

Dr. Tackett is a pharmacologist and a professor of pharmacology and Toxicology at the University of Georgia. Dr. Tackett reached the same conclusion as Dr. Howard with respect to the causation of Bourne's anophthalmia. His opinion is based upon "(1) the known pharmacological/ toxicological actions of Benlate which have been demonstrated to produce anophthalmia; (2) exposure to Benlate at a critical time in Mrs. Bourne's pregnancy; and (3) the fact that dermal absorption of Benlate results in systematic levels of benomyl and its metabolites in humans." (Tackett report at 1.)

A. Mrs. Bourne's exposure to Benlate

Dr. Howard estimated the amount of Benlate to which Mrs. Bourne was dermally exposed, and Dr. Tackett adopted the estimate. Based upon Mrs. Bourne's deposition transcript, Dr. Howard opined that 30% of Mrs. Bourne's skin was exposed to 5% of the gallon of Benlate mixture each time she applied the Benlate to her plants every 10 to 12 days. The 5% figure, Dr. Howard testified, represents "how much liquid . . . [is necessary] to achieve the level of wetness which [Mrs. Bourne] described in her deposition." (Howard Dep. at 255.)[3] He also testified,

[3] While Dr. Howard was deposed on a number of occasions, the deposition transcript representing the first 5 dates on which he was deposed appear on consecutively numbered pages. References to these first 5 dates (October 30, 1998; October 31, 1998; December 10, 1998;

(Continued on following page)

however, that he engaged in back-calculation to arrive at the 5% figure, stating that the 5% is an "estimate of the volume of Benlate mixture in a one gallon can that would need to be splashed onto Mrs. Bourne to achieve 20 percent per billion[4] of benomyl equally distributed throughout her body with a dermal transmission rate of 3.5 percent of the dose." (*Id.* at 117.)

The 5% of a gallon, which is 225 milliliters,[5] or 225,000 microliters, was spread, Dr. Howard opines, over 30% of Mrs. Bourne's body. (*Id.* at 331.) Mrs. Bourne's body surface area, based upon her height and weight, is found by him to be 15,000 square centimeters, with 30% thereof being 4,500 square centimeters. (*Id.* at 332.) Dr. Howard opines that Mrs. Bourne's dermal exposure to Benlate mixture was 50 microliters per square centimeter, or 12.5 micrograms of benomyl per square centimeter. (*Id.* at 332-333.)[6]

December 11, 1998; and April 30, 1998.) will hereinafter be referred to as "Howard Dep. at . . ." Dr. Howard's most recent deposition was taken on October 4, 2001, and the transcript of the deposition begins anew with page number 1. References to the October 4, 2001, deposition transcript will be designated by date and page.

[4] He likely intended to say "parts per billion" rather than "percentage per billion," with 20 parts per billion being the minimum concentration of benomyl which several *in vitro* studies found to be the lowest effect level for cells dosed with benomyl. *See infra* III.C. Dr. Howard has adopted the EPA-utilized 3.5% dermal absorption rate for benomyl through human skin.

[5] In his deposition, he estimated a UK gallon to be at 4500 milliliters, leading to the 225 figure. A UK gallon is actually 4546.09 milliliters, with 5% thereof being 227.3.

[6] It appears that Dr. Howard used primarily volume measures in his depositions and metric weight measurers in his report. Using metric weight, Dr. Howard concluded that the weight of 5% of the benomyl

(Continued on following page)

Dr. Howard admits that these figures are not measured values, but are estimates based upon Mrs. Bourne's deposition testimony. (*Id.* at 333-334.) Dr. Howard conducted no testing or measurements to arrive at his figures. (*Id.* at 255, 295, 331-34, 670-71.) He is unsure how much, if any, of the purported 50 microliters per square centimeter of the Benlate mixture either ran off of Mrs. Bourne's skin or was rubbed off onto her clothing. (*Id.* at 337-38.) He did not address a published study conducted by DuPont examining dermal exposure to Benlate in a home garden setting which concluded that dermal exposure to benomyl using two gallons of Benlate containing approximately 9.5 grams of benomyl in a compression sprayer was less than 1 milligram of benomyl. *See* Leighton P. Everhart & Richard F. Holt, *Potential Benlate Fungicide Exposure During Mixer' Loader Operations, Crop Harvest, and Home Use*, 30 J. Agric. Food Chem. 222 (1982) ("DuPont Everhart study"). Converting 1 milligrams to 1,000 micrograms and dividing by 4,500, the number of square centimeters of Mrs. Bourne's body Dr. Howard contends was exposed to the Benlate mixture, then dividing by 2 to account for the study's use of 2 gallons, one is left with a figure of .11 micrograms per square centimeter. Dr. Howard's estimate of 12.5 micrograms per square centimeter exceeds this figure by about 113 times. (Howard Dep. at 333.) Nor did he address a study conducted by the National Institute for Occupational Safety and Health ("NIOSH") which found that nursery workers engaged in

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present in the UK gallon was 56.25 milligrams, with a total amount deposited per square centimeter on Mrs. Bourne's skin at 10,000 nanograms. (Howard report at 3.)

weighing, mixing, and applying Benlate with compression sprayers are exposed to between .14 and .19 micrograms of Benlate per square centimeter per hour on the thigh and lower leg. Hoekstra, Kiefer, and Tepper, *Monitoring of Exposure to Benomyl in Nursery Workers*, 38:8 J. Occup. Environ. Med. 775,779 (1996) ("NIOSH Hoekstra study") Dr. Howard's estimate of 12.5 micrograms per square centimeter would exceed the range found in that article by 66 to 89 times. Aside from a failure to address at least the NIOSH study, Dr. Howard points to no study supporting his calculation.

B. Dermal Absorption

The estimate of the dermal transmission rate of benomyl into human blood varies based upon the source. DuPont's expert, Dr. Howard I. Maibach, opines that the human dermal absorption rate for benomyl is less than 1%, whereas the United States Environmental Protection Agency ("EPA") has adopted a 3.5% dermal transmission rate and the California EPA refers to a 10% dermal transmission rate.[7]

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[7] Based upon the court's review of documents generated by the EPA's Hazard Identification Assessment Review Committee, on behalf of the Office of Pollution Prevention: Pesticides and Toxic Substances, the 3.5% dermal absorption rate and the referenced dermal dosage levels of benomyl appear to be utilized by the EPA merely for "the risk assessment for benomyl, and its primary metabolite carbendazim [MBC]." It does not appear that the EPA has made determinations about benomyl and its causation of teratogenic effects in humans. See Memorandum dated March 20, 2001, from Deborah Smegal, Toxicologist, entitled, "Benomyl and Carbendazim-Endpoint Selection for Incidental Oral Ingestion for Carbendazim."

The dermal absorption rates of both the EPA and the California EPA are based upon rat studies. The EPA's figure is based upon a study conducted in 1978-79 by Belasco involving the dermal absorption of benomyl on rat skin. In this study, the dermal absorption rate was 3.5% after 10 hours at a .1 milligram dose, but with lower absorption rates for lesser time intervals.[8] The study found that the dermal absorption rate decreased as the doses of benomyl applied to the skin increased. (Ex. 29-30, Def.'s Mot. Exclude.) The California EPA's dermal absorption rate appears in a 1999 document entitled Benomyl (Benlate) Risk Characterization Document. The document states that it "assumes" a 10% dermal absorption rate based upon another California EPA report prepared in 1998, entitled *Estimation of Exposure to Persons in California to Pesticide Products that Contain Benomyl*, by David Haskell and Louise Mehler. The 1998 report, referring to the Belasco rat study, utilizes a 10% dermal absorption rate. (Ex. 27-28, Def.'s Mot. Exclude.)

Based upon his estimation that Mrs. Bourne was dermally exposed to 56.25 milligrams of Benlate with each use, Dr. Howard calculated Mrs. Bourne's total amount of benomyl absorption using several different dermal absorption rates.[9] With a 5% transmission rate, 500 nanograms

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[8] In the Belasco study, the dermal absorption level after 4 hours was 1.7% at a .1 milligram dose, .3% at a 1 milligram dose, .04% at a 10 milligram dose, and .03% at a 100 mg dose. After 10 hours of dermal exposure, the amount absorbed was 3.5% at a .1 milligram dose, .5% at a 1 milligram dose, and .09% at a 10 milligram dose, and .03% at a 100 milligram dose.

[9] He testified at deposition that the "rate" is in "a nontemporal context." (Howard Dep. at 119.)

per square centimeter would be absorbed; with a 3.3% transmission rate, 330 nanograms per square centimeter would be absorbed, and with a 2% transmission rate, 200 nanograms per square centimeter would be absorbed. (Howard report at 2.) Assuming Mrs. Bourne has a blood volume of 4 liters, and converting nanograms to milligrams and then dividing by one million, Dr. Howard concluded that the amount of benomyl absorbed by Mrs. Bourne was 562, 375, or 225 parts per billion, with 5%, 3.3%, and 2% dermal absorption rates, respectively. (Howard Dep. at 361-62.) DuPont contends that there is no reliable evidence underlying Dr. Howard's use of these dermal absorption figures inasmuch as they are based solely on rat studies. Indeed, DuPont points out, plaintiff's own benomyl dermal absorption study, referred to below, lends no support to Dr. Howard's contention. It appears to be the only such study of living humans.

Plaintiff nevertheless asserts that in addition to the California EPA rat dermal absorption study finding a 10% dermal absorption, a study conducted for plaintiffs by TNO ("TNO study") in the Netherlands and led by W. Mueling, involving human dermal absorption of benomyl, provides "compelling evidence" of a dermal transmission rate of at least 3.5%. (Pl.'s Resp. Motion to Exclude Howard and Tackett at 28.) Drs. Howard and Tackett address the TNO study generally in their reports to state that the study provides evidence that benomyl applied dermally becomes bioavailable.[10] In the TNO study, the skin of eight

[10] Bioavailability is a term used to indicate the extent to which a chemical reaches tissues or bodily fluids, such as blood plasma, and is available to be transported throughout the body.

adult human volunteers was dosed with 60 milligrams of Benlate solution, containing approximately 30 milligrams of benomyl, on both upper thighs for a four hour period. The blood of the test subjects was collected via canula for 6 hours following exposure, with the urine of the subjects collected for 72 hours following exposure. (TNO study at 3, attached as exhibit 36, Def.'s Motion to Exclude.) Urine and blood samples were also taken prior to Benlate administration. (*Id.*)

The study was conducted in two phases. In the first phase, the samples were analyzed by high performance liquid chromatography ("HPLC") to detect and measure benomyl metabolites MBC, 5-HBC, and STB. (Mueling Dep. at 74-76.) MBC is the only benomyl metabolite that Drs. Howard and Tackett believe to be teratogenic. (Howard Dep. at 240, 401-02; Howard 10/04/01 Dep. 97-98; Tackett Dep. at 59.) Specifically, 5-HCB is not claimed by Drs. Howard and Tackett to be teratogenic. (*Id.*)

No MBC or STB was detected in any blood sample and only 1 of 176 blood samples had a detectable, but non-quantifiable, level (i.e., a trace) of 5-HBC. (TNO study at 3.) 5-HBC was detected and measured in the urine samples. (*Id.*) In the second phase of the test, half of the blood and urine samples were reanalysed using a more sensitive detection method called liquid chromatography-tandem mass spectrometry. (Mueling Dep. at 74-76.) MBC was detected in some plasma samples but not at quantifiable levels. (*Id.*) Again there were detectable amounts of the benomyl metabolite 5-HBC found in the urine excreted for up to 72 hours following exposure.

However, the highest levels of MBC detection were found in blood plasma samples taken prior to benomyl

administration, and urine samples from four of the testing subjects tested positive for 5-HBC prior to any benomyl administration. (TNO study, Appendix 3) Mueling "speculate[s]" that the pre-dose benomyl metabolite detection could be the result of food ingested by the test subjects prior to the commencement of the study. (Mueling Dep. at 59-60.) Mueling testified that he only subtracted pre-exposure amounts of 5-HBC found in the urine and MBC found in plasma from the amounts of these metabolites found post-exposure when the pre-exposure amounts were deemed to be "significant." (*Id.* at 73-76.) On some test subjects, the amount of 5-HBC found pre-exposure was subtracted from the post-exposure amount, and on others it was not. (*Id.*) No amounts of pre-exposure MBC in plasma were subtracted from post-exposure MBC amounts. (*Id.*)

Mueling testified that no conclusions could be drawn from the second portion of the study and that other than listing those results in the TNO study report, he did not use the results for any other purpose. (*Id.* at 75-77.) The first portion of the study found "the plasma levels did not reach the limit of detection [and] [w]hat cannot, therefore, be determined from this investigation is the degree of skin exposure at which plasma levels of benomyl would have become detectable, which (naturally) would occur when the clearance rate of the liver was being exceeded." (TNO study at 24.)

It is the presence of the 5-HBC metabolite in the test subjects' urine samples which Drs. Howard and Tackett contend support their 3.5% dermal absorption rates for Benlate on human skin. Dr. Howard contends that the 5-HBC evidences the amount of benomyl that had at one time been absorbed through the skin of the test subjects

before being excreted in their urine. (Howard 10/04/01 Dep. 53-64.) Despite the fact that no quantifiable MBC was found is the plasma of the test subjects, Dr. Howard, using the respective molecular weights of 5-HBC and the benomyl metabolite MBC, took the measured amounts of 5-HBC present in the test subject's urine to calculate what he contends is the amount of benomyl that was absorbed through their skin to become bioavailable in the form of MBC in their blood. (Howard 10/04/01 Dep. at 61.) While his specific mathematical computations of the back-calculation of 5-HBC to MBC[11] are not made a part of the record in this case, based upon this back calculation, Dr. Howard contends that a 3.5% dermal absorption rate is "conservative." (*Id.* at 62-63.) Dr. Tackett adopted Dr. Howard's calculations of the amount of benomyl bioavailable in the subjects of the TNO study. (Tackett Dep. at 211, 224.)

C. Teratogenicity

In addition to concluding that Mrs. Bourne was exposed to benomyl which was absorbed into her body through her skin, Drs. Howard and Tackett opine that benomyl is a human teratogen, capable of causing the plaintiff's anophthalmia. They rely upon *in vivo*[12] studies, involving injections of Benlate into laboratory rats and *in*

[11] These computations were apparently exhibits to his October 4, 2001, deposition but were not submitted to the court.

[12] *In vivo* tests are conducted on living animals.

vitro[13] studies, examining the effect of Benlate on living human cells, for their assertions that benomyl is a human teratogen. The first *in vivo* study relied upon by Drs. Howard and Tackett was conducted by Dr. Robert Staples in 1980 and involved benomyl administration via stomach tube to pregnant rats at doses of 3 milligrams, 10 milligrams, 30 milligrams, 62.5 milligrams, and 125 milligrams per kilogram of body weight per day. (Ex. 9, Def.'s Mot. Exclude.) In the first of two *in vivo* studies by Dr. Staples, both sponsored by DuPont, 2 of 251 rats at the 10 milligram dose level bore offspring with micropthalmia.[14] At the 30 milligram level, 1 of 238 offspring had micropthalmia, and at the 62.5 milligram level, 10 of 213 offspring had micropthalmia. This study concluded that the lowest effect dose of benomyl appeared to be 10 milligrams per kilogram of weight per day. (*Id.*) In the second study, Dr. Staples found a lowest effect dose, or lowest observable effect level ("LOEL"), at 62.5 milligrams per kilogram of weight. A no observable effect level ("NOEL") of 30 milligrams per kilogram per day was adopted by Dr. Staples based upon the second study.

Drs. Howard and Tackett cite to another rat gavage study conducted by a professor at the University of California in 1991 which revealed ocular abnormalities in 43% of rat offspring at a dose level of 62.4 milligrams per kilogram of weight. E. Hoogenboom, *Effects on the Fetal*

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[13] *In vitro* tests involve the exposure of isolated cell systems to a particular substance under controlled laboratory conditions within a test tube or petri dish.

[14] Micropthalmia, a condition related to anophthalmia, involves being born with underdeveloped eyes.

Rat Eye of Maternal Benomyl Exposure, 10 Current Eye Research 7, 601-612 (1991) (Ex. 12, Def.'s Mot. Exclude.) Another rat gavage study performed by Culick in 1981 wherein 125 milligrams per kilogram per day of benomyl were injected into pregnant rats revealed teratogenic effects. Robert Culick, *Determination of Benomyl/Methyl-2Benzimidazole Carbamate (MBC), 4-OH MBC and 4-OH MBC Concentration in Maternal Blood and in the Concepti of Rats Exposed to Benomyl by Gavage*, Haskell Report No. 970-80. Finally, a whole body autoradiography study ("Covance study"), sponsored by DuPont, revealed a concentration of benomyl in the uveal tract, the area lining the inside of the eye behind the cornea. Whitby, C-Benomyl: *Quantitative Whole Body Autoradiography Following Oral Administration (2mg/kg) to Female Pigmented Rats*, Covance Laboratories (1998) (Ex. 49, Def.'s Mot. Exclude.)

In addition to using *in vivo* rat studies to support their contention that benomyl is a human teratogen, Drs. Howard and Tackett also used *in vitro* tests. Dr. Howard relies upon *in vitro* tests conducted by Dr. Dick Van Velzen and Dr. Graham McLean. Dr. Tackett relied only on the *in vitro* study of Dr. McLean. Dr. Van Velzen, in studies performed in 1996 and 1997, dosed human fetal lung cells, fibroblasts, in varying concentrations of Benlate for a period of 24 hours. He then examined the cells to ascertain the smallest amount of Benlate concentration at which there was any observable effect on the cell through micronuclei[15] formation, and in 1997, through both micronuclei

[15] Dr. Van Velzen described micronuclei as simply "very small nuclei." (Van Velzen Dep. at 73.)

formation and DNA reduction. (Van Velzen Dep. at 73.) Van Velzen inferred that cell death, or aptosis, was occurring based upon the increased formation of micronuclei and a reduction in DNA. *Id.* at 74. Van Velzen found a LOEL at 25 parts per billion benomyl. (Van Velzen Dep. at 298.) He found a NOEL at 20 parts per billion benomyl. (*Id.* at 300-303.)

Dr. McLean, in a similar *in vitro* study conducted in 1997, exposed human cancer nerve cells, neuroblastomas, and rat cells, to benomyl of varying concentrations for 24 hours. (McLean Dep. at 77-78.) He reported a LOEL for the rat cells at .3 parts per billion benomyl. McLean, et al., *The Effect of Benomyl on Neurite Outgrowth in Mouse NB2A and Human SH-SY5Y Neuroblastoma Cells In Vitro*, NeuroToxicology 19 (4-5):629-631 (1998).

Based upon these *in vitro* and *in vivo* tests, Drs. Howard and Tackett inferred that benomyl is a human teratogen and extrapolated the human threshold dose for teratogenicity.

D. Epidemiology

In reaching their opinions with respect to causation, Drs. Howard and Tackett considered three epidemiological studies relating to Benlate exposure and birth defects, but rejected those studies as irrelevant and unreliable, based upon the opinions of plaintiff's expert epidemiologist, Dr. David Ozonoff.

1. Spagnolo study

A 1994 study by A. Spagnolo was conducted "following the report of clusters of anophthalmia and microphthalmia

in England and Wales and their possible relation to the pesticide Benomyl." *See* A. Spagnolo, et al., *Anophthalmia and Benomyl in Italy: A Multicenter Study Based on 940,615 Newborns,* Repro. Toxicology 8:397-403, 397 (1994). In this study, the authors utilized registries of birth defects to identify 111 children with anophthalmia and microphthalmia born in Italy between 1986 and 1990, of a total of 940,615 births. After controlling for defects associated with chromosomal abnormalities, the authors divided Italy into regions and examined the relationship between incidence of birth defects and use of benomyl by region. The results revealed a negative, nonsignificant coefficient, with there being a negative relationship between increased benomyl use by region and the incidence of anophthalmia and microphthalmia. *Id.* at 401. In a second phase of the study, the authors examined the relationship between parental occupation and the incidence of children with anophthalmia and microphthalmia and found "no significant association between agricultural occupation and anophthalmia and microphthalmia at birth." *Id.* at 401.

Dr. Ozonoff contends that the Spagnolo study is "incapable of providing information on the risks of anophthalmia/microphthalmia to the offspring of exposed pregnant women from Benlate exposure." (Ozonoff report at 5.) He maintains that the study does not examine, as does the typical ecologic correlation analysis, the relationship between prevalence of exposure in relation to prevalence of a health outcome inasmuch as the study does not measure individual exposure to benomyl, but only examines benomyl's prevalence by region in Italy. (*Id.*) He contends that the results are "fundamentally uninterpretable in terms of the risks of Benlate to individuals."

(*Id.* at 9.) Dr. Ozonoff does not mention the second portion of the study examining parental occupation and its relationship to anophthalmia and microphthalmia except to state in a conclusory manner that parental occupation is likely to be misclassified. (*Id.* at 12.)

2. Kristenson study

In a study published in 1997, the authors examined the relationship between the prevalence of birth defects as reported to the Medical Birth Registry of Norway from 1969 to 1989 out of a total of 192,417 births, and parental occupations in farming. The study found significant correlations between parental occupation in farming and several birth defects, but not eye malformations. P. Kristenson, et al., *Birth Defects Among Offspring of Norwegian Farmers*, Epidemiology 8:537-44 (1997). In a letter to the editor of the British Medical Journal, Kristenson described this study and its results. The letter states:

> Benomyl was introduced in Norway in 1971. It is mainly used as a fungicide in greenhouses and orchards; it is also used to a limited extent during the spring in fields of vegetables and, since the mid-70s, in the late autumn in the grain fields. Its use has been limited in Norway: the maximum sale was 1682 kg active compound in 1980. We considered farm activities after 1970 that might result in exposure of benomyl at a relevant time: work in greenhouses throughout the year; in orchards for children conceived in April-June; with vegetables grown in fields for children conceived in August-November. Eleven percent (n=21843) of the entire cohort of infants born in 1967-91 had potentially been exposed to benomyl according to these criteria. Four of the

> 192416 [sic] children had been diagnosed as having anophthalmia or microphthalmia.

Kristenson, P. "Clusters of anophthalmia: No link with benomyl in Norway." BMJ, 308:206-207, 1994.

Dr. Ozonoff asserts that the Kristenson study is invalid because the use of Benlate in Norway was very restricted and because of the possibility of the failure to recognize less conspicuous forms of microphthalmia and cases in which microphthalmia is a concomitant malformation. (Ozonoff Rep. at 11.)

3. Dolk study

A study examining geographical variation in anophthalmia and microphthalmia in England published in 1998 investigated the allegations of an English newspaper that there were "clusters" of blind children in England in farming areas associated with Benlate use. H. Dolk, et al., *Geographical Variation in Anophthalmia and Microphthalmia in England,* 1988-1994, British Medical Journal, 317:905-09. The study found that the overall prevalence of anophthalmia and microphthalmia in England was 1 in 10,000 births and found no statistically significant variation from region to region of England. *Id.* at 907.

Dr. Ozonoff does not discuss the Dolk study specifically in his report but merely states, "the existing data from England and Norway is similarly without relevance

to this question [the risk of anophthalmia and microphthalmia to the offspring of exposed pregnant women to Benlate]."[16]

Dr. Howard and Dr. Tackett both relied upon Dr. Ozonoff's opinions regarding the irrelevance of the epidemiological studies relating to Benlate use and anophthalmia and microphthalmia. (Howard report at 1.) Inasmuch, however, as Dr. Ozonoff failed to address the second, more relevant, portion of the Spagnolo study involving the relationship between parental occupation and the incidence of children with anophthalmia and microphthalmia except to state in a conclusory manner that the parental occupation is likely to be misclassified, and considering he provided only conclusory and speculative remarks about the Kristenson study and the Dolk study,[17] it appears that the wholesale rejection by Drs. Howard and Tackett of these epidemiological studies was unfounded.

III.

DuPont seeks to exclude the testimony of Drs. Howard and Tackett on several grounds. DuPont asserts that (1) Drs. Howard and Tackett are not qualified to render the opinions they offer; (2) they failed to perform a differential diagnosis of the plaintiff; (3) the methodologies of Drs. Howard and Tackett of relying upon single-species high

[16] Dr. Ozonoff testified that at the time he drafted his report on September 28, 1999, he had not read the Dolk study, which had not yet been published. (Ozonoff Dep. at 19.) He testified that reading the study did not alter his opinion. (*Id.* at 19-20)

[17] Indeed when he drafted his report, he had not read the Dolk study.

dose animal studies and *in vitro* cell culture tests, without relying upon relevant epidemiological data, to draw conclusions about human teratogenesis via dermal absorption, is not scientifically valid, reliable, or generally accepted pursuant to Federal Rules of Evidence 104, 402, and 702; (4) Dr. Howard's calculations of the dose of Benlate to which Mrs. Bourne was exposed, and Dr. Tackett's ratifications thereof, are imprecise and invalid; (5) the dermal absorption rates utilized by Drs. Howard and Tackett were derived using unreliable and scientifically invalid bases; and (6) Drs. Howard and Tackett misuse EPA and EU regulatory processes and recommendations as if they were causation determinations.

In response, plaintiff asserts that, while each piece of data underlying the conclusions of Drs. Howard and Tackett may not be sufficient to independently justify the experts' conclusions, taken as a whole the body of data relied upon by Drs. Howard and Tackett support their conclusions, rendering their methodologies sound.

IV.

Effective December 1, 2000, Federal Rule of Evidence 702 was amended to reflect the United States Supreme Court's landmark decision of *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). The revised Rule 702 states:

> Testimony by Experts – If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based

> upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed. R. Evid. 702. As the Advisory Committee Notes indicate, the amendment to Rule 702 is consistent with the district court's "gatekeeping" function as articulated in *Daubert*. The proponent of the proposed expert testimony must establish its admissibility by a preponderance of proof. *See Daubert,* 509 U.S. at 592 n.10; Fed. R. Evid. 104(a).

In *Daubert*, the United States Supreme Court charged trial judges with the responsibility to act as "gatekeepers" to "ensure that any and all scientific testimony . . . is not only relevant, but reliable." *Daubert*, 509 U.S. at 589. As a part of its analysis, a trial court is to determine "whether the expert is proposing to testify to (1) scientific knowledge that (2) will assist the trier of fact to understand or determine a fact in issue." *Id.* at 592. It is for the trial court to make the "preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." *Id.* at 592-93. As to the first prong of the inquiry, whether the expert offers "scientific knowledge," the analysis focuses on whether the subject of the expert's testimony is grounded in the "methods and procedures of science," and constitutes "more than subjective belief or unsupported speculation." *Id.* at 590. In order to qualify as "scientific knowledge," an inference or assertion must be derived by the "scientific method." *Id.* That is, the testimony must be supported by " 'good grounds,' based on what is known." *Id.*

The Supreme Court in *Daubert* set forth a flexible, non-exhaustive checklist of four factors for trial courts to utilize in their evaluations of reliability. *Id.* at 593-94. These factors include: (1) whether a theory or technique can be or has been tested; (2) whether it has been subjected to peer review and publication; (3) whether a technique has a high known or potential rate of error and whether there are standards controlling its operation; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community. *Id.* at 592-94. In a later opinion, the Court further emphasized that these factors are flexible, not rigid, may or may not be pertinent in a given case and are to be applied based upon "the particular circumstances of the particular case at issue." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 150 (1999).

The second prong of the *Daubert* analysis focuses on whether the expert's testimony will be helpful to the trier of fact in deciding a fact in issue. Included in that analysis is the question of relevancy or "fit." *Id.* at 591. The expert's proferred scientific testimony must be sufficiently tied to the facts of the case that it will be of assistance to the factfinder in resolving a disputed fact. *Id.* (citing *United States v. Downing*, 753 F.2d. 1224, 1242 (3rd Cir. 1985)). That is, there must be a "valid scientific connection to the pertinent inquiry" before the testimony is admissible. *Id.* at 591-92.

The Court noted in *Daubert* that "vigorous cross examination, presentation of contrary evidence and careful instruction on the burden of proof are traditional and appropriate means of attacking shaky but admissible evidence." *Daubert*, 509 U.S. at 596. However, when making the determination as to admissibility, a trial judge

has considerable leeway in both the determination of reliability and the means the judge uses to make it. *See Kumho Tire Co.*, 526 U.S. at 152.

The court does not propose to question the qualifications of Drs. Howard and Tackett for purposes of this order.[18] The court must determine, pursuant to *Daubert*, first, whether the proffered testimony constitutes "scientific knowledge," grounded in the "methods and procedures of science," and is "more than subjective belief or unsupported speculation," and second, whether the proffered testimony "fits" with the factual inquiry of the case. *See Daubert*, 509 U.S. at 589-91.

A. General Causation

Drs. Howard and Tackett have derived their general causation theory, that benomyl is teratogenic to humans, based solely upon *in vivo* rat gavage studies and *in vitro* tests. They discredit the only existing human data, consisting of epidemiological studies reflecting no statistical relationship between potential Benlate exposure and human birth defects. They also disavow gavage benomyl testing on different animal species – the mouse and the

[18] In a rather factually similar civil action, *E.I. DuPont De Nemours & Co., Inc. v. Castillo*, 748 So.2d 1108 (Fla. 3d DCA), *review granted*, (Fla. 2000) ("*Castillo*"), wherein plaintiff alleged that his mother's dermal exposure to Benlate caused his anophthalmia, the intermediate appellate court of Florida excluded the testimony of Dr. Howard but found nonetheless that he was qualified under the Florida Rules of Evidence to render his proffered opinions. The Florida Supreme Court granted certiorari and oral arguments were presented on February 6, 2001.

rabbit – which have revealed no ocular abnormalities in the offspring.

There can be no dispute that properly designed and conducted animal testing can yield relevant and useful information in the field of human toxicology. *See, e.g., Turpin v. Merrell Dow Pharmaceuticals, Inc.*, 959 F.2d 1349, 1360-61 (6th Cir. 1992), *cert. denied*, 506 U.S. 826 (1992) ("We do not mean to intimate that animal studies lack scientific merit or power when it comes to predicting outcomes in humans. Animal studies often comprise the backbone of evidence indicating biological hazards, and their legal value has been recognized by federal courts and agencies. Here, the record's explanation of the animal studies is simply inadequate. . . . The record fails to make clear why the varying doses of Bendectin or doxyalamine succinate given to the rats, rabbits and *in vitro* animal cells would permit a jury to conclude that Bendectin more probably than not causes limb defects in children born to mothers who ingested the drug at prescribed doses during pregnancy."). Likewise, *in vitro* tests provide useful information about metabolic processes at a cellular level, and may supplement existing animal and human data. *See, e.g., Allen v. Pennsylvania Engineering*, 102 F.3d 194, 198 (5th Cir. 1997) (*in vitro* data shows only that ethylene oxide has mutagenic and genotoxic capabilities in living organisms, not that it necessarily causes brain cancer in humans). However, the extrapolations of Drs. Howard and Tackett, from high-dosage, single species *in vivo* testing and lengthy benomyl exposure *in vitro* testing, to conclude that benomyl is a human teratogen and to establish the levels at which it is alleged to be teratogenic, are neither reliable, pursuant to the first prong of *Daubert*, nor relevant, under the second prong.

Courts considering the reliability of experts' extrapolation to human teratogenicity from *in vivo* and *in vitro* tests have recognized that such tests are generally considered to be suspect when relied upon for that purpose. In the absence of other strong indicators of the reliability of *in vivo* and *in vitro* tests, including supporting epidemiological studies, testing on closely related species,[19] and the use of comparable dosages, courts have overwhelmingly found unreliable the methodology of extrapolating human teratogenicity from *in vivo* and *in vitro* tests. *See, e.g., Raynor v. Merrell Pharms., Inc.*, 104 F.3d 1371, 1374 (D.C. Cir. 1997) (concluding it was not methodologically sound for experts to draw inference from chemical structure studies, *in vivo* animal studies, and *in vitro* studies, that Bendectin caused human birth defects, when epidemiological evidence was to the contrary); *Allen*, 102 F.3d at 198 (excluding expert testimony as unreliable where *in vivo* tests were inconclusive and *in vitro* tests could not be extrapolated to establish human teratogenicity); *Conde v. Velsicol Chem. Corp.*, 24 F.3d 809, 813 (6th Cir. 1994) (finding experts were unable to connect chemical chlordane with plaintiffs' injuries using *in vivo* and *in vitro* tests, in light of plaintiffs' low level of exposure to the substance and contradictory epidemiological evidence); *Sorensen v. Shaklee Corp.*, 31 F.3d 638, 646 n.12 (8th Cir.

[19] Primates are considered to render the most persuasive results with respect to extrapolation of the results to humans, followed by other mammals, then birds, followed by reptiles. *See* Erica Beecher-Monas, *The Heuristics of Intellectual Due Process: A Primer for Triers of Science*, 75 N.Y.U. L. Rev. 1563, 1608 (2000) (citing I arry C. Gilstrap & Bertis B. Little eds, *Drugs and Pregnancy* 9 (2d ed. 1998) (noting that "nonhuman primates are better predictors . . . than are nonprimate models because they are phylogenetically close to humans")).

1994) ("Because of the dose-response differential between animals and humans, however, extrapolating to humans from animal studies is problematic."); *Turpin*, 959 F.2d at 1360-61 ("The record fails to make clear why the varying doses of Bendectin or doxyalamine succinate given to the rats, rabbits and *in vitro* animal cells would permit a jury to conclude that Bendectin more probably than not causes limb defects in children born to mothers who ingested the drug at prescribed doses during pregnancy.");[20] *Richardson v. Richardson-Merrell, Inc.*, 857 F.2d 823, 830 (D.C. Cir. 1988), *cert. denied*, 493 U.S. 882 (1989) (finding that chemical structure activity analysis and *in vitro* and *in vivo* studies used by plaintiff's expert cannot furnish sufficient foundation for causation opinion in the face of considerable contrary epidemiological evidence); *Lynch v. Merrell-Nat'l Labs.*, 830 F.2d 1190, 1194 (1st Cir. 1987) (*in*

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[20] The court in *Turpin*, referring to an authoritative text on teratology, explained why animal testing cannot be directly extrapolated to human beings:

> "A recognized text on teratology states the customary scientific view that 'it has become axiomatic in experimental teratology that agents capable of causing any adverse biological effects can usually also be shown to be embryotoxic under the right conditions of dosage, developmental stage, and species susceptibility,' and that 'virtually all drugs and a great range of chemicals can indeed be shown to be embryotoxic under appropriate laboratory conditions. . . . The author concludes that to 'eliminate drugs and chemicals because they can be shown to be embryotoxic at high dosage would be unacceptable' because to do so 'would eliminate most drugs and many useful chemicals upon which modern society depends heavily.'")

Turpin, 959 F.2d at 1359 (quoting James Wilson, Current Status of Teratology, in *Handbook of Teratology* 60 (J. Wilson & C. Fraser, eds. 1977)).

vivo and *in vitro* animal tests and the tests on "analogous" chemicals, whether "singly or in combination, do not have the capability of proving causation in human beings in the absence of any confirmatory epidemiological data"); *Wade-Greaux v. Whitehall Laboratories, Inc.*, 874 F. Supp. 1441, 1484 (D. Vi 1994), *aff'd.*, 46 F.3d 1120 (3rd Cir. 1994) (excluding causation experts' opinion, finding high dose animal testing and *in vitro* animal test data are not relied upon by experts in the field of teratology for extrapolating the results found directly to the human experience); *In re Agent Orange Product Liab. Litig.*, 611 F. Supp. 1223, 1241 (E.D. N.Y. 1985), *aff'd*, 818 F.2d 187 (2d Cir. 1987), *cert denied*, 487 U.S. 1234 (1988) ("[L]aboratory animal studies . . . are generally viewed with more suspicion than epidemiological studies, because they require making the assumption that chemicals behave similarly in different species.").

The only existing epidemiological evidence[21] is contrary to plaintiff's position. Further, *in vivo* benomyl testing has revealed ocular abnormalities in only a single species of animal, whereas gavage testing on both the rabbit and the mouse revealed no ocular abnormalities.[22]

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[21] Drs. Howard and Tackett rely upon the opinion of Dr. Ozonoff, a physician and environmental epidemiologist, discrediting the validity of the epidemiological evidence relating to benomyl. Even assuming this methodology – reliance upon the opinion of an expert in the field of epidemiology – is sound, the plaintiff has no epidemiological evidence supporting the proposition that benomyl is a human teratogen. He is left, therefore, with only rat gavage tests and *in vitro* tests to extrapolate both human teratogenicity of benomyl and the levels of the substance capable of causing birth defects. *See supra* II.D.

[22] *See* R. Kavlock, et al., *Teratogenic Effects of Benomyl in the Wistar Rat and CD-1 Mouse, with Emphasis on the Route of Administration*,

(Continued on following page)

The court concludes that Drs. Howard and Tackett have failed to offer sufficient support for the otherwise suspect single-species *in vivo* tests and *in vitro* tests to render methodologiocally sound an extrapolation of human teratogenicity.

Moreover, the rat gavage studies and the *in vitro* tests relied upon by Drs. Howard and Tackett, using injections of high-levels of benomyl directly into the stomach of rats and high-level *in vitro* dosing of cells of both rats and humans in benomyl for 24 hours, do not "fit" with the facts of the case as alleged. *General Elec. Co. v. Joiner*, 522 U.S. 136 (1996), is germane. In *Joiner*, a city electrician who suffered from lung cancer filed suit against the manufacturer of polychlorinated biphenyls (PCBs) and manufacturers of electrical transformers and dielectric fluid, alleging strict liability, negligence, fraud, and battery. The district court excluded the testimony of electrician experts and granted defendants' motion for summary judgment. The United States Court of Appeals for the Eleventh Circuit reversed. The Supreme Court considered the fact that the plaintiff's proffered causation expert relied upon

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Toxicol. Appl. Pharmacol., 62:44-54 (1982) (Ex. 11, Def.'s Mot. Exclude); W. Busey, Segment II – *Teratology Study in Rabbits*, Hazleton Leboratoris, Inc. (Unpublished Report No. MRO 1079) (1968) (Ex. 13, Def.'s Mot. Exclude); S. Munley, *Developmental Toxicology Study of DPX-T1991-529 (Benomyl) in Rabbits*, Newark, Delaware, E.I. DuPont de Nemours and Co., Inc., Haskall Laboratory Unpublished Report No. HLR 164-95) (1995) (Ex. 14, Def.'s Mot. Exclude).

Dr. Tackett acknowledged at deposition that one species of animals will generally have a different teratogenic response to a chemical than will another animal species. (Tackett Dep. at 224.) Dr. Howard testified, "[i]t's usually said that to define something as a human teratogen it's desirable to have two animal models." (Howard Dep. at 672.)

studies indicating that infant mice developed cancer of a different type than the plaintiff, after receiving massive gavage doses of PCBs. *Id.* at 144. The Court noted that the experts never explained "how and why [they] could have extrapolated their opinions from animal studies "far removed" from the circumstances of the plaintiff's exposure to PCBs." *Id.* Finding the studies upon which the experts relied to be "not sufficient, whether individually or in combination, to support their conclusions," the Court found that the district court had not abused its discretion in excluding their testimony. *Id.* at 146.

Similarly, the rat gavage testing relied upon by Drs. Howard and Tackett is "far removed" from the plaintiff's alleged exposure, with high doses of benomyl injected directly into the rats' stomachs. Using the Staples studies as an example, the lowest level of benomyl injection at which an ocular effect on offspring was noted was at 10 milligrams per kilogram of weight per day. A comparable dosage for Mrs. Bourne, who weighs approximately 50 kilograms, would be a direct injection (setting aside the fact that the chemical is alleged to have been absorbed dermally at a rate of 3.5%) of 500 milligrams, or one-half of one gram. Each sachet of Benlate contained approximately 1.19 grams of benomyl (based on 53% of the 2.25 gram Benlate sachet). Thus, to be comparable to the lowest observable effect level, approximately one-half of the contents of a sachet would have to be injected into Mrs. Bourne. The other rat studies relied upon by Drs. Howard and Tackett involved far greater injections of

benomyl.[23] Indeed, none of the rat studies producing teratogenic effects involved exposure to benomyl dermally or orally. With respect to the *in vitro* tests wherein cells were continually soaked in benomyl for 24 hours, plaintiff has made no contention that Mrs. Bourne was continually and directly exposed to benomyl for such an extended period. In sum, the analytical gap between the rat evidence relied upon by Drs. Howard and Tackett and the inferences drawn therefrom is simply too wide, rendering the extrapolations a poor "fit" for the facts of the case.

The court concludes that the methodologies of Drs. Howard and Tackett in concluding that benomyl is a human teratogen are unsound.

B. Specific causation

Even assuming, *arguendo*, that the extrapolations from *in vivo* rat studies and *in vitro* studies to human teratogenicity levels were scientifically sound, the court nonetheless concludes that the opinions of Drs. Howard and Tackett relating to specific causation are not scientifically valid and reliable.

It appears that the conclusion of Dr. Howard, as adopted by Dr. Tackett, with respect to Mrs. Bourne's level of dermal exposure to Benlate, is highly speculative, without the indicia of reliability required by Rule 702 and *Daubert*. Rather than conducting any type of test or study

[23] Staples second rat study produced a LOEL at 62.5 milligrams per kilogram; the Culick study injected 125 milligrams per kilogran; the Hoogenboom study used 62.4 millograms per kilogram of weight. *See supra* p. 15-17.

to attempt to recreate the actions described by Mrs. Bourne in her deposition with respect to treating her plants with Benlate, it appears that Dr. Howard has developed arbitrary figures to represent what he deems to be the percentage of Mrs. Bourne's body exposed to Benlate and the amount of the Benlate mixture applied to her skin which he calculates to be 5% of the one-gallon Benlate mixture used periodically by her. While he contends on the one hand that the figure is based upon the portion of a gallon estimated by him as necessary to produce the level of wetness described by Mrs. Bourne, he also testified that he back-calculated the amount of dermal benomyl exposure necessary, using a 3.5% dermal absorption rate, to achieve a benomyl concentration of 20 parts per billion. (Howard Dep. at 117.) Thus, Dr. Howard's 5% figure is, at best, purely speculative and at worst, devised to ensure that a certain desired end – 20 parts per billion – was met. In either case, the adopted methodology, or lack thereof, is contrary to principles of sound scientific method. *See, e.g.*, *General Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) ("nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* [an assertion made but not proved] of the expert"); *Oglesby v. General Motors Corp.*, 190 F.3d 244, 250 (4th Cir. 1999) ("A reliable expert opinion must be based on scientific, technical, or other specialized knowledge and not on belief or speculation, and inferences must be derived using scientific or other valid methods.").

Additionally, the 5% figure does not take into account pertinent published studies (DuPont Everhart study and NIOSH Hoekstra study, *supra* p. 8-9) examining the exposure of garden users to Benlate. *See, e.g.*, *Cooper v.*

Smith & Nephew, Inc., 259 F.3d 194, 203-04 (4th Cir. 2002) (affirming trial court's exclusion of plaintiff's causation expert, in part, on basis that expert rejected, without offering sound explanation, medical literature and plaintiff's own medical records which tended to support another cause of plaintiff's condition). Nor is the 5% calculation capable of being tested or reproduced. *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 592-94 (1993) (setting forth non-exhaustive list of factors pertinent to whether an opinion is reliable); *United States v. Dorsey*, 45 F.3d 809, 814-815 (4th Cir. 1995) (affirming exclusion of expert testimony as scientifically invalid because the methodology upon which it was based was not generally accepted, had never been peer-reviewed, and its potential rate of error was high). In sum, Dr. Howard's methodology in arriving at the 5% figure, is unreliable.

The methodology utilized by Drs. Howard and Tackett in deriving a level of human dermal absorption for benomyl likewise appears to be unsound. In his report, Dr. Howard utilized several dermal absorption rates, the lowest thereof being 2%. He identifies several sources for the dermal absorption rates, including the EPA's use of a 3.5% rate and the amount of Benlate "potentially absorbed" by the test subjects in the TNO studies. The EPA's use of a 3.5% figure is based upon a 1979 study on the dermal absorption of Benlate on rat skin wherein 3.5% was absorbed after a period of 10 hours. *See supra* p.9. Setting aside the fact that it is not alleged that Mrs. Bourne was exposed to Benlate for a 10 hour period, it is well established among the scientific community that rat skin is more permeable than human skin. (*See* Maibach Aff. at ¶ 48; Tackett Dep. at 126-27.) Dr. Tackett testified in his deposition that he believes that rabbit skin and rat

skin are approximately 10 times more permeable than human skin with respect to Benlate or beromyl. While his report does not identify a specific rate which he has adopted, it mentions the EPA's 3.5% dermal absorption rate, based on rat studies, and formulated for risk assessment, not causation, purposes. (Tackett Report at 4.) The only study relied upon by Drs. Howard and Tackett relating to the dermal absorption of benomyl on living human skin is the TNO study conducted by Mueling.[24] (*See* Mueling, TNO Lab Reports V3596 and V2662.) Mueling testified at deposition that based on the TNO study he was not able to determine a rate of benomyl transmission through the human skin, nor was he able to ascertain whether the rate of percutaneous absorption of benomyl is dependent upon the amount of skin which is exposed. (Mueling Dep. at 77.) The TNO study found no measurable amounts of benomyl metabolites in the blood plasma of the test subjects. (*See* W. Mueling, TNO Lab Reports *supra* 38.)

Despite the seeming lack of useful results produced by the TNO study,[25] Drs. Howard and Tackett rely upon the

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[24] A study conducted on human cadavers revealed a dermal absorption rate for benomyl of less than 1%. (ICI Central Toxicology Laboratory, Report CTL/P/3659.)

[25] Meuling testified that the TNO study failed to determine the following: the rate of transmission of benomyl through human skin; the levels achieved of the major metabolites of benomyl in blood plasma; the time it takes for benomyl metabolites to reach a peak concentration in blood plasma or how long that peak concentration persists; the speed or time at which the level of benomyl metabolites begin to drop off; the half-life of benomyl metabolites in blood plasma; whether the rate of percutaneous absorption of benomyl is dependent on or changes with the amount of skin exposed; whether the rate of percutaneous absorption of benomyl was dependent on or changed with the amount of

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detectable amounts of 5-HBC in the test subjects' urine to calculate what they contend to be the dermal bioavailability of benomyl. They back-calculate the cumulative amount of benomyl and its metabolite MBC that passed through the blood and tissue of the human test subjects in the TNO study by converting the total amount of 5-HBC found in the urine of the test subjects, assuming benomyl is approximately 138% of the molecular weight of 5-HBC. (Howard Dep. at 83-85.) As DuPont's expert pharmacologist and toxicologist Michael Owens, PhD, points out, this methodology is based on the "unsupported assumption that all of the 5-HBC in the urine was at one point benomyl/MBC in the blood plasma or tissue." (Owens Aff. at ¶ 7a.) It ignores the possibility that benomyl/MBC was metabolically converted to 5-HBC in the skin, prior to reaching the blood. (*Id.*) The skin's conversion of benomyl to 5-HBC, is, according to Dr. Owens, the "most likely" scenario, supported by the lack of any measurable amount of benomyl or MBC found in the blood of the TNO test subjects. (*Id.*) Further, the back-calculation fails to account for the amounts of 5-HBC which were detected in the urine, or for that matter the MBC detected in the plasma, of the test subjects prior to administration of Benlate. *See supra* II.B.

It appears that the back-calculation of 5-HBC to benomyl is internally inconsistent with the very TNO study upon which Drs. Howard and Tackett purport to rely. The conductor of the study, Mueling, testified at deposition that one cannot ascertain the amount of MBC

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substance (dose) applied to a given area; and any kinetic parameters for benomyl in humans. (*See* Meuling Dep. at 76-78.)

or 5-HBC in the blood based on the TNO urine data. (Mueling Dep. at 107-08.) Mueling also testified that his TNO study did not reveal a rate of transmission through human skin. (*Id.* at 76-78.) The court concludes that the calculations of Dr. Howard, adopted by Dr. Tackett, purporting to reflect the rate of human dermal absorption of benomyl into the blood based upon the amount of 5-HBC found in the urine of the TNO test subjects constitutes merely the "*ipse dixit*" of Drs. Howard and Tackett and not grounded in "the methods or procedure of science." *See General Elec. v. Joiner*, 522 U.S. at 146.

Whether derived from the molecular weight of irrelevant 5-HBC metabolites in TNO test subjects' urine or extrapolated directly from the 20-year old Belasco tests involving the administration of benomyl to permeable rat skin for extended durations, the 3.5% dermal absorption rate used by Drs. Howard and Tackett cannot be said to be methodologically sound.

VI.

It appearing that the opinions proffered by Drs. Howard and Tackett meet neither the requisite standards of reliability or relevance under Federal Rule of Evidence 702, as set forth by the United States Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993) and its progeny, the court concludes that their testimony must be excluded.

Wherefore, for the foregoing reasons, it is ORDERED that DuPont's motion to exclude the testimony of Dr. Howard and Dr. Tackett be, and it hereby is, granted.

The Clerk is directed to forward copies of this order to all counsel of record.

DATED: January 11, 2002

/s/ John T. Copenhaver, Jr.
JOHN T. COPENHAVER, JR.
United States District Judge

UNITED STATES COURT OF APPEALS

FOR THE FOURTH CIRCUIT

FILED
February 23, 2004

No. 02-1469
CA-97-90-2

ANDREW BOURNE, a minor by and through his parents, next friends and natural guardians, Chris Bourne and Maggie Bourne

Plaintiff-Appellant

v.

E. I. DUPONT DE NEMOURS & COMPANY, d/b/a DuPont, a Foreign Corporation

Defendant-Appellee

TRIAL LAWYERS FOR PUBLIC JUSTICE

Amicus Curiae

ORDER

Appellant has filed a petition for rehearing.

The Court denies the petition for rehearing.

Entered for a panel comprised of Judge Widener, Judge Niemeyer, and Judge Gregory.

For the Court,

/s/ Patricia S. Connor
CLERK